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WORLD POPULATION PROBLEMS AND BIRTH CONTROL

BY

C. G. Hartman (*Conference Chairman*), M. A. Breckenridge, R. C. Cook, C. B. Darner, M. E. Davis, H. F. Dorn, C. S. Ford, C. J. Gamble, J. S. Gillam, A. F. Guttmacher, G. W. Hunter, J. MacLeod, C. McLane, N. Millman, F. W. Notestein, W. T. Pommerenke, M. S. Rothnem, A. Stone, W. B. Stromme, and W. S. Thompson

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Editor
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WORLD POPULATION PROBLEMS AND BIRTH CONTROL*

Conference Chairman: C. G. Hartman

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PREFACE

By Carl G. Hartman

Ortho Research Foundation, Raritan, N. J.

A review of the titles of the papers in this monograph leads me to quote one of the epigrams of Omar Khayyam in the inimitable *Rubaiyat*, as rendered by Fitzgerald:

> "*Happy the soul, having come, soon goes*
> *But crowned with peace is he that never came.*"

This profound observation was made a thousand years ago. If Omar Khayyam were living in his native Iran today and witnessed the abject poverty and overcrowding of Asiatic peoples and the consequent slender thread on which hang the precarious lives of hundreds of millions, I wonder if he would count "happy" those born in such a difficult environment, though perhaps we must acknowledge that every soul experiences a bit of happiness, even here on earth. To his observation as poet and philosopher, "But crowned with peace is he that never came," Khayyam might have applied his knowledge of mathematics. I like to think that if he were living now he would function as a statistician and demographer, colleague of the authorities who took part in the Conference on which this monograph is based.

The science of population studies is a highly-specialized branch of biology, so it is quite fitting that the Conference should have been sponsored by the Section of Biology of The New York Academy of Sciences as a part of its effort.

INTRODUCTION

By Frank W. Notestein

Princeton University, Princeton, N. J.

Our epoch would seem to have very little of which it can be proud. Overshadowing all else is the fact that we have participated in wars of unexampled horror and destruction. On one score, however, we shall surely be given great credit. We have achieved a degree of conquest over disease unrivalled in human history. An appreciable sector of the human race can now expect that half of those born will live more than seventy years. In times when each daily paper carries casualty lists, we tend to forget this fact. It is hard to realize, but nevertheless true, that in the Western world the peacetime progress in health since 1900 has saved many more lives than the wars have cost. In spite of its huge losses in this century, the Western world has many more people surviving than it would have had with no wars and a perpetuation of the death rates of the year 1900. With all its failings, our epoch has shown the way in which mankind can, if it chooses, reduce the toll of sickness and death to levels undreamed of a few decades ago.

Yet, by curious inversion, our achievements contain the seeds of their own limitation. We have been so preoccupied with the problems of saving life that we have failed to recognize the dangers of its superabundance. Today, as the powerful techniques of sanitation and epidemic control save lives in the densely crowded areas of agrarian poverty, we face rates of population growth that greatly complicate all efforts to achieve the sustained advances in living levels that the attainment of full health requires.

As a whole, the biological and medical professions which have given us such powerful means to limit death have been slow to devote attention to the development of equally powerful means for the control of birth. Without birth control, however, the means to limit death cannot in the long run reach full effectiveness. It gives me great pleasure, therefore, to open a biological and medical monograph based on a conference on birth control with special emphasis on world population problems.

POPULATION AS A WORLD PROBLEM

By Warren S. Thompson

Scripps Foundation for Research in Population Problems, Miami University, Oxford, Ohio

It is disturbing to hear people speak of population as a world problem, because they may be giving a wrong impression of the nature of the really urgent population problems facing the world today. It is especially disturbing when the population problem of the world is put in the form of a question, asking, "Can the people of the world produce enough food to provide for the 20–25 million persons being added to the world's population each year?"

There can be no doubt whatever that the population problems which confront many peoples are world problems, in the sense that the way in which these problems are handled, or ignored, does affect the welfare of the people in a large part of the world. As a matter of fact, we must recognize that when it is a matter of taking some practical action with regard to urgent population problems, we do not yet live in "one world." Rather than a single world population problem, there are many population problems that need attention today, and these problems, arising in different areas and countries, all have distinctive features that require different treatment. Although we live in a world in which famines and extreme poverty in any particular country, especially one which has a large population, raise problems which affect the welfare of a considerable portion of mankind, we are not yet able to function as a unified world. Because of the lack of adequate world organization, one nation, without intending to, may contribute to the perpetuation of poverty and hardship in another by passing a new tariff act, by imposing exchange restrictions, or adopting import quotas. The United States, for example, may make it more difficult and perhaps impossible for India to continue the export of certain raw materials by a tariff act. As a consequence, thousands of Indian farmers may fall into poverty, lose their precarious hold on land that furnishes their entire existence, and India may be required to forego certain very essential imports. In such cases, the people of India are just as unable to participate in an international effort which will eliminate sudden and serious disturbances in their economy as the people of the United States are unable to participate in any effective effort which will prevent the recurrence of famine and lead to the abolition of poverty among the Indians. In the writer's opinion, therefore, it is a dangerous oversimplification to think of "one" world-population problem.

Let me make my position on population as a world problem more concrete by looking a little further into the consequences of independent conduct in India and the United States, with regard to particular events. India has had two rather severe famines in the past eight years (1943 and 1951). It is well-known, and no people are more insistent on the fact than the Indians themselves, that the great mass of their people live near subsistence level. The margin between current production and the consumption necessary for mere sustenance of life at a very low level is always so small that, every year, many millions of people die because of undernourishment. It follows that when crops are only a little below the average there is real famine. This is true among a majority of the world's people.

In this situation, the only action which can be taken by the United States, or any other nation, at a time of famine in the non-industrialized countries is to supply the food which will keep the people alive until the next harvest, in the hope that it will be larger. It is obvious, however, that as long as a country is subject to recurrent famines, supplying relief food from time to time is no solution of the fundamental problem faced by that country. The only solution is an increase in production sufficiently rapid to insure a larger margin between production and the consumption essential to sustain life. This can be done in only two ways: (a) by speeding up the people's production capacity until it attains a rate of growth well beyond that of population and (b) by reducing the rate at which the people reproduce, or, better yet, by effecting these two changes simultaneously. In neither respect is any outside people free to take action. Matters affecting economic development and population growth are regarded as domestic concerns only. The governments of the poverty-stricken countries are, in general, disposed to hold that their chief problem is one of increasing production and/or securing new outlets for emigration. The more industrialized peoples are likely to insist that the reduction of fertility is also a matter of prime importance if the hardships inseparable from a high death rate are to be avoided. When the problems are stated in these terms it is clear that outside peoples are virtually estopped from taking any action genuinely helpful to the poverty-stricken nations of the world.

The manner in which one nation may unintentionally aggravate the population problem of another may be illustrated as follows. If the United States has been buying certain products from India for some time, *e.g.*, jute for bags, and, for any reason, places a new tariff on such imports, or raises the existing tariff, or if some other country adopts import quotas for certain Indian products substantially below previous imports, these actions may result in such a sharp reduction in the sales of these products that the entire economy of the country is adversely affected. The injured country can protest such arbitrary action, if it appears to violate some agreement between the two countries, but such a protest will probably be "rejected," because we regard our tariff action as a purely domestic concern above treaty agreements, just as India regards any action to increase production or reduce reproduction as a purely domestic matter in which outside aid or advice is accepted only after careful examination and in a form which will not compromise the recipient's freedom of action.

As a matter of fact, the only ways in which we are quite free to take action to influence population growth in backward industrial areas are ways which will almost certainly be highly harmful to these areas in the long run. We are free to send famine relief and thus keep people alive at a time of famine and we are relatively free at all times to furnish the means to improve public health work which will reduce the death rate and thus lead to a still more rapid increase in population. These efforts to reduce the death rate are generally welcomed everywhere, but any effort to increase production, if it is on a scale likely to have any appreciable effect on the nation's total income, is seldom proffered by an outside country, or its nationals, unless it promises a profit to individuals or an increase of political power to the nation offering it. The motive for such action is always suspect, therefore. This is not surprising when we consider the character of colonialism in the past and the means which have been used to insure the safety of the investments of foreigners in non-military, non-industrialized lands.

Some of the leaders, moreover, in these non-industrialized countries, are not convinced that small increases in total production will have an alleviating effect on the hardships of life where population is already dense and where the level of living is very low. Such men are more or less aware that increased production often leads to an increase in numbers and that the rigid structure of their economy makes a steady and rapid improvement in production extremely difficult. They are, however, very reluctant to give careful consideration to the reduction of the birth rate and almost certainly will not accept assistance of this kind from the outside.

As far as one can judge, however, there are only a few leaders among the non-industrialized peoples who realize the likelihood of population increases consuming practically all of the prospective increases in production. The great majority of them are quite as unaware of any essential connection between population growth and increases in production as were the foreigners who took a hand in the exploitation of colonial areas. Consequently, it is not likely that any very serious effort will be made in the near future in most non-industrialized areas, either from within or without, to reduce fertility and thus help to insure increased *per capita* production. The emphasis will continue to be placed on raising production faster than increases in population, without any clear realization of the reciprocal causal relations which exist between population growth and increase in production.

Such indifference to changes in economy and social organization which affect the growth of population and thus lead to future difficulties may be seen in the colonial areas of Asia during the past half century. In order to make colonies "pay," it was necessary to maintain peace within them, improve transportation, introduce some health service (at least in the areas of most intense exploitation), undertake famine relief, provide a better diet for the laborers where fairly steady work was needed, and invest enough capital to secure greater efficiency in the production and preparation of raw materials for market. It was also essential that a fairly efficient administration of the law be established in the exploited area. Little or no thought was given to the consequences of these "improvements" on the growth of population.

This indifference to the demographic consequences of colonial action in no way detracted from its effectiveness as a stimulant of population growth, through the ensuing reduction of the death rate. As a result, the growth of population in many colonial areas in recent decades has been quite similar to that in Western Europe in the early and middle decades of the nineteenth century. India (including Pakistan) grew from about 256 millions in 1872 to about 429 millions in 1951 (assuming that Pakistan grew at the same rate as the Indian Union between 1941 and 1951). The Philippines have grown from about 7.6 millions in 1903 to about 19.2 millions in 1948, and Java from 28 millions in 1900 to about 49 millions in 1950. In China, where there has been almost constant turmoil and strife in many areas during the last century, it seems doubtful whether there has been any substantial population growth, except in Manchuria. China's growth in the past five to seven decades certainly has not been comparable to that in those colonial areas where an effective government and a small improvement in public health work and possibly in economic conditions, have led to lower death rates and hence, to a moderately rapid population increase.

It is impossible, of course, to prove either that the level of living has shown a slight rise, or has declined, as is so often claimed by the natives interested in such matters. It is likewise impossible to assign a definite proportion of the decline in the death rate to either health work or better economic conditions. The writer finds it very difficult to believe, however, that the very modest health services in most colonial areas and even in Japan could have resulted in a reduction of the death rate sufficient to permit the increases in population which have actually taken place, if there had not also been some improvement in the living conditions of a significant portion of the population. It would, of course, be folly to say that improvement in health conditions alone could not reduce the death rate, but the writer thinks that the maintenance of peace and the improvement of economic conditions have generally done more to encourage population growth than the development of a public health service.

Whatever the reason, the point to consider here is that there has been a fairly rapid increase in population in many of these industrially backward areas during the past few decades as total production has increased, although a great many people who try to look at the matter without prejudice are not convinced that the living conditions of the mass of the people have risen to any significant extent. There is good reason to think that practically all of the increases in economic production that have taken place have gone toward the support of a larger population under the "do nothing" policy concerning population growth that has prevailed in these colonial areas and in other non-industrialized areas. The most reasonable expectation for the foreseeable future, moreover, assuming the continuance of a "do nothing" policy, is that future increases in production will also be used in the same manner. It will require several decades to at best make effective any restrictive policy. Admittedly, there is a large element of uncertainty in this situation but the writer submits that the above is the most reasonable guess that can be made with the data now at our disposal.

At the beginning, the fact was introduced that the population problems which arise in many countries do impinge upon the life of people in other countries because the economy of the world has been unified in certain respects by the development of modern transportation and communication. Every country needs more and more raw materials and manufactures from other countries as its economy becomes more complex, and, as a consequence, it becomes more and more dependent upon other countries in certain respects and is affected directly by the supplier's economic and political vicissitudes. There is no escape from this increasing interdependence. A famine in India, a reduction in the rubber crop in Malaya, a ground-nut scourge in West Africa, or a blight on the coconut crop in the islands of the Western Pacific, as well as political instability everywhere, have their repercussions in a large number of countries. We cannot ignore such events. Nor can we ignore the fact that population is increasing in many of the industrially backward areas of the world and that these areas are finding it very difficult to increase production rapidly enough to care for this increase in population and raise the level of living as people expect it to be raised. The consequences of such a situation cannot be foretold with any great assurance because the efforts which may be made by any country to solve what it regards as its population problem are closely allied to its conduct in meeting other internal and external situations. At any given moment, the world population status is not the world's population problem so much as the population problem of Italy, Germany, Japan, India, *etc.*, and the way in which each problem affects the other peoples of the world. The leaders of the several countries, of course, see their own population problems in the setting of the political, economic, and social relations of their respective countries with other peoples, as well as in terms of the exigencies of internal politics.

That is not to say that the efforts of Japan, Italy, or Germany to expand their empires are due solely, or even largely, to their population problems. I do believe, however, that the difficulties already encountered, or clearly foreseeable, in providing a better living for an increasing population, also provided these peoples with a strong motive for the expansion of empire. When this motivation was reinforced by many other urges toward expansion it may well have had a greater influence on the decision to expand than the facts warranted. We can never know the relative importance of the many different factors at work. Even if the motivation provided to expansionist groups in these countries by the growing difficulties of providing a better living to larger numbers was of minor importance, it was there, nevertheless. The fact that it was largely ignored by the political leaders of other countries did not prevent it from becoming a rather powerful tool in the hands of Hitler, Mussolini and Tojo in carrying their people with them in planning the expansion of their empires. The population problem of a particular country can therefore be thrust upon us as a world problem and, even though we may ignore it for a time, we may nevertheless find that the methods used to resolve it become a decisive element in determining our lives. Think of the many ways in which the conduct of Japan since 1931, and particularly since 1937, has exerted a decisive influence upon our own lives.

I believe that if the population problems of Japan played only a minor role in determining her expansion it was a role sufficiently important to merit our careful study and force us to ask ourselves whether we can afford to be indifferent to population growth in any country or area large enough and powerful enough to undertake forcible expansion. Is the population growth of the United States, India, Japan, or the Soviet Union purely an internal affair, when this growth, in some cases encouraged by their leaders, can be used as an argument by them for the seizure of larger resources? That is not to say that India, Java, or some other country will follow in the foot-steps of Germany or Japan, but as long as the populations of these nonindustrialized countries grow at a rate about equal to their increases in production while the wants of their people increase at a faster rate because of increased contact with ways of better living, and as long as there are large differentials in resources to satisfy these growing wants, there are likely to be attempts on the part of some of the peoples growing in power to seize the resources which will enable them to live better.

Since I believe that the real problems of population with which we are concerned arise in particular countries and under particular conditions, I am not very concerned with a world problem of population usually posed in the form of the question of whether the world can supply means of subsistence for its increasing numbers. I believe that such a problem is a meaningless abstraction. It must be divided into a hundred concrete questions or problems, to which we can obtain reasonable and useful answers, even if they are not as exact as we could wish. I will illustrate this statement by a few questions regarding the population problem of India. To give meaning to these questions, I must state a few facts briefly.

India (including Pakistan) has had an increase in population since 1921 amounting to about 135 millions. This is about three times as great as the increase in the preceding fifty years. This increase has come about, to the best of our knowledge, because of a decrease in the death rate which, in turn, is to be attributed to an increase in production and a modicum of public health service. There is no clear evidence of any change in the birth rate, either increase or decrease, during recent decades. As far as the data permit us to judge, it appears that the crude birth rate is in the neighborhood of 43–45 per 1,000 per year. The death rate appears to have varied from 33–35 in the decade from 1921–31, from 28–30 in the decade 1931–41, and to have held at 30–32 in the last decade. (It is assumed that the movements of vital phenomena were the same in Pakistan as in the Indian Union in the decade 1941–51.) In the five decades preceding 1921, three showed a rate of increase of less than one per cent, one was six per cent, and the other was nine per cent.

The first question follows. Since India's population has increased approximately 44 per cent in the past three decades and, since there is no sign of a decline in the birth rate and very considerable efforts are being made to reduce the death rate still more, what population growth is India likely to experience during the next several decades?

The most reasonable answer that can be given to such a question, in the light of our present knowledge, is that the population of India will grow for several decades approximately as fast as subsistence increases. Since the experience of the Western world and Japan is that the voluntary control of births is practised most quickly in populations which have enjoyed a substantial rise in the level of living and that it is, in some measure, a response to the desire to maintain and improve the higher level of living attained, especially in relation to the opportunities of their children, any reduction in the birth rate of India seems some distance away, under a "hands off" policy there or in any other agrarian society.

A deliberate public policy to encourage the control of population growth might hasten the decline of the birth rate in India or any other non-industrialized area, but there is no information now available to justify the belief that the birth rate in such countries can be substantially reduced in a few years, while there is much evidence that the conditions which seem necessary to initiate birth control will immediately lead to an even more rapid decline in the death rate. There can be little doubt that an increase of a few tens of millions of dollars spent on public health service, even in a great country like India, would have a very large effect in further reducing the death rate, if the necessities of life could be increased at the same time. An excellent example of the effect of a relatively small additional expenditure on public health in reducing the death rate is the virtual eradication of malaria in Ceylon in two or three years, with a reduction in the average death rate from 21.3 for the years 1943–46 to a rate of 13.4 in the years 1947–49. Since the recorded birth rate in the years 1943–47 averaged 38.2 and was even higher (39.9) in the years 1947–49, we see that the rate of natural increase rose from 17.0 in the years 1943–46 to 26.5 in the years 1947–49. Whether the increase will continue at a rate which may double the population in 27 years will depend primarily on similar increases in production of the necessities of life for the Ceylonese. There can be no improvement in the level of living in Ceylon unless the annual increase of production exceeds the 2.65 per cent increase in population or unless the birth rate falls. The possibility of a decline in the death rate is much the same in India as in Ceylon. In addition, the data for Ceylon suggest a rise in the birth rate if a great scourge like malaria can be controlled. Even if the birth rate of India should rise by one point, it would add about 420,000 persons to her population growth each year.

No country in which the people live close to the subsistence level can support an increase of population without an increase in production of approximately the same percentage. If we wish to acquire a realistic conception of population growth in India during the next few decades, therefore, we must not only evaluate the effects of the changes in the death rate which may arise from the control of disease through public health work, but we must also try to evaluate what is likely to happen to India's production, especially her food supply.

There is a vast amount of pertinent agricultural knowledge available which, if put to use within a few years, would enable India or any other undeveloped area to increase agricultural production quite rapidly. Enough is known about the means by which the production of India's staple crops can be raised 50 to 100 per cent to make this possible within a few years. The next question follows. Is there a likelihood of any such improvement being realized within a few years or even within three or four decades? Japan required approximately 50 years to double her yields, and I am convinced that the general milieu in Japan in 1870 was more favorable for rapid improvement in agricultural production than the milieu of India today. If we assume, however, that India's agricultural production can be doubled in 30 or 40 years, this does not mean that the level of living will rise substantially during this period, and that this improved level of living will automatically reduce the birth rate. Japan's population was approximately doubled in the fifty-year period during which her agricultural yields were about doubled. The level of living for a considerable part of Japan's population also rose substantially during this period because her industry was expanding rapidly and her *per capita* production was increasing. These are accepted facts. Why should we not suppose that the same thing will happen in India?

This leads us to another question. Can India become industrialized as rapidly as Japan? At present, India is somewhat more industrialized than Japan in 1870. Why should not India become industrialized during the ensuing 50 years even faster than Japan became industrialized between 1870 and 1920?

At the time when the modernization of the economy of Japan became a national policy (about 1870), Japan possessed a strong central government which was prepared to assist in the modernization of industry and agriculture in every possible way. Japan also possessed a few wealthy families which were stimulated and encouraged to enter into many new fields of industry and commerce by the prospect of large profits. As a consequence, the industrialization of Japan proceeded at a rate which is without parallel, prior to the five-year plans of the Soviet Union. At the same time, there was a substantial improvement in the level of living and, by 1920, the birth rate of the rapidly-increasing urban population was declining.

Both political conditions and the system for the distribution of the national income in Japan were very favorable for the rapid expansion of industry, much more favorable, I believe, than the situation in India today. I doubt if we can reasonably hope for a rapid industrialization of India unless conditions become settled more rapidly and unless the Colombo plan and the Point Four program take hold much more effectively than now appears likely. India also lacks homogeneity in population, custom and culture to follow the leadership of a few people, as was the case in Japan.

The industrial system which India must adopt today is far more complex and far more costly to install than that which Japan installed when she began her industrialization. I am not questioning the ability of the Indians, or any of these other non-industrialized peoples, to operate a complex industrial system. India is in a more difficult situation than Japan was 75 years ago, however, in need for capital, trained personnel, men experienced in international trade, and unity in national economic policy. It is only logical to assume that India's industrialization will be quite slow under the best of conditions. Religion, caste, and certain climatic limitations may also retard the development of Indian industry and commerce, compared to Japan. We know comparatively little about these factors, but they may prove to be decisive elements in determining the speed of development of Indian industry and commerce.

I will reiterate that the more successful India becomes during the next two or three decades in increasing agricultural and industrial production, extending trade, and providing good health for her people, the more rapid will be the growth of population. This being the case, there is a strong probability that the proportion of her production devoted to raising the general level of living will be quite small. With the health knowledge we possess today, it would be easily possible for India's population growth during the next few decades to exceed by one-half that of Japan during an analogous period of her development. Witness the situation in Ceylon. It is also possible that the differences in culture between the two countries will lead to a slower reduction of the birth rate in India than in Japan, unless there is a deliberate and intelligent effort on the part of the Indian Government to encourage the reduction of the birth rate and unless this is so managed that the people are persuaded to adopt effective practices soon and on a wide scale.

Each of the questions posed here can be broken down into several, more specific questions. The same type of questions may be asked in considering the development of population in any non-industrialized country but the answers would vary considerably in detail. The population problem of India does differ in many respects from that of China, and that of Japan differs greatly from both of these. This is what I mean when I say that there is no world population problem, but there are many population problems confronting the peoples of the world. Some are much more difficult to solve than others and some are much more urgent. There is little hope of dealing wisely with most of them, however, until we study each one carefully and thus prepare ourselves to think and act rationally in relation to the adjustment of numbers and resources in each particular case. We have been, and still are, too much inclined to think that increase in production is the answer to all problems caused by the pressure of people on their resources. We must also realize that there may be too many people for existing resources and that the least wasteful way to attain a good level of living for all will require that we reudce the birth rate just as we reduce the death rate.

THE EFFECT OF PUBLIC HEALTH DEVELOPMENTS UPON POPULATION GROWTH

By Harold F. Dorn
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The world, in particular the part inhabited and controlled by the western Europeans and their descendants, has just passed through a 400-year boom, unique in the annals of written history, which Walter Prescott Webb has called the Age of the Frontier and whose termination is marked by the passing of the last great frontier of the earth.[1] Although the surface of the earth still is not completely occupied, there are no new frontiers in sight comparable to that which has just been passed, nor are we likely soon either to expand the earth or to discover a new world comparable to it. At the beginning of this era, around 1500, the population of Europe undoubtedly did not exceed 100,000,000, perhaps 15 to 20 per cent of the total population of the world, and occupied a territory of roughly 3,750,000 square miles, about seven per cent of the land area of the earth. Near the end of the era, around 1900, the descendants of this population numbered nearly 550 million, made up approximately one-third of the world's population and occupied or controlled five-sixths of the land area of the world.

They had seized and peopled two great continents, North and South America, and one smaller continent, Australia, with its adjacent island, New Zealand; had partially peopled and entirely controlled a third great continent, Africa; and had dominated southern Asia and the neighboring islands. The English-, French- and Spanish-speaking peoples led in the occupation and exploitation of the last great frontier, the lesser roles being played by the Dutch, Belgians and Portuguese.

Among these, the English-speaking people held the dominant position at the end of the era. No one knows the number of English-speaking persons around 1500 but it almost certainly could not have exceeded four or five million.[2] By 1900, these people numbered about 129 millions or eight per cent of the population of the world. In addition, they occupied or controlled one-third of the land area of the earth and, together with the non-English-speaking inhabitants of this territory, made up some 30 per cent of the total population.

The Age of the Frontier was characterized by an unprecedented increase of population, a several-fold expansion of the land base for this population and a hitherto-undreamed-of multiplication of capital in the form of precious metals, goods and commodities. Most important of all, the augmentation in capital and usable land proceeded more rapidly than the growth of population. Although any estimate of the relative rate of growth of population, usable land and capital during this era, can be little more than a rough guess at best, Webb has reckoned that, during the 400 years between 1500 and 1900, the people of European origin increased somewhat more than five-fold, contrasted with a six-fold increase in land and a 104-fold increase in capital expressed in gold and silver. The growth of capital in the form of goods and commodities cannot be measured but almost certainly it dwarfed the increase in land and precious metals.

A situation equally favorable for a rapid growth in population, associated with an even more rapid improvement in the standard of living, does not appear likely for those peoples of the world who did not participate in the boom just described. These people, in particular those inhabiting Asia (outside of the Soviet Union), make up slightly more than one-half of the total population of the world. They have almost entirely thrown off the political domination of Europeans and look forward hopefully to achieving the level of living hitherto enjoyed only by people of European descent. The prospect of repeating the demographic history of the Europeans seems very dim. To understand why this is true, let us examine, in more detail, some of the factors in the demographic revolution of the people of European origin.

All biological organisms must adapt themselves to their environment if they are to continue to survive either as individuals or as a species. Man is no exception to this general principle of adaptation. Unlike other biological organisms, however, man, to an increasing degree, can modify and control his environment.

This partial control over environment is relatively recent in the history of mankind. Throughout most of the centuries of its existence, the human race undoubtedly has had a birth rate, which, if unrestrained, would have resulted in "standing room only" throughout the world many centuries ago. Until very recently, however, this excessive fertility has been controlled, just as in all other forms of life, by an almost equally high mortality. The size of the population in any area has been held in check by war, pestilence and privation.

That this must have been so can be illustrated by a simple arithmetical computation. At present, the total population of the world is estimated to be increasing at the rate of about one per cent per year. If their ancestors had always increased at this same rate, the present population of the world could have developed from the offspring of a single couple whose first child was born about the time of Julius Caesar.

It is easy to forget how recently man has gained control of pestilence and privation and that, even now, this control is restricted to a minority of the world's population. About 1750, the death rate in London is thought to have been between 40 and 50 per 1,000 population.[3] Until about 1800, burials were more frequent than christenings during most years, so that the population was maintained only by migration from rural areas. Even though reliable statistics are not available, the death rate for other large European cities must have been comparable to that of London. In rural areas and small towns, the death rate probably varied from a low of 25 to 35 per 1,000 population to much higher rates during years of famine or epidemics.

It was not until the middle of the nineteenth century that the people of western Europe finally freed themselves from the specter of famine. Walford listed 201 famines in the British Isles between 10 A.D. and 1846.[4] The last great famine of western Europe occurred during 1846–47 in Ireland. The shortage of food there which followed the blight of the potato crop lasted nearly six years. In spite of the assistance provided by England and the United States, the total mortality from all causes during the five years ending in 1851 is estimated at nearly 1,000,000 persons, or one-eighth of the population of Ireland just before the famine.[5] In addition, large numbers emigrated to the United States, so that the census of 1851 revealed a decrease of about 1,500,000 in total population during the decade following 1841.

Disease waged a close struggle with famine for first place as regulator of population growth. Hecker estimated that perhaps one-fourth of the population of Europe died during the Black Death epidemic around the middle of the fourteenth century.[6] The last serious epidemic in England was the Great Plague of London during 1664–65. At least one-sixth of the population of London is estimated to have perished.[7] This proportion is probably a serious understatement, since many people fled from the city during the epidemic.

TABLE 1

ESTIMATED POPULATION OF THE WORLD, BY MAJOR REGIONS, 1650–1950 (IN MILLIONS)

Date	*World*	*Africa*	*America*	*Asia*	*Europe*	*Oceania*
1650	545	100	13	330	100	2
1750	728	95	12	479	140	2
1800	906	90	25	602	187	2
1850	1,171	95	59	749	266	2
1900	1,608	120	144	937	401	6
1920	1,834	136	207	997	485	9
1930	2,008	155	244	1,069	530	10
1939	2,195	175	274	1,162	573	11
1949	2,378	198	321	1,254	593	12

Estimates for 1650–1900 are from Carr-Saunders[10]; those for 1920–1949 are from Demographic Yearbook, 1949–50, published by the United Nations[11].

Coming to more recent times, Lorimer has estimated that from 25 to 30 million extra deaths occurred in Russia during the 13-year period, 1914–1926, as a result of war, famine and disease.[7] This number was about one-fifth of the official population at the end of 1926.

During all the centuries of its existence, the human race had gained only slowly in numbers prior to 1650, the date of the first acceptable estimate of the total population of the world. At that time, about 545,000,000 persons inhabited the earth (TABLE 1). No one knows how reliable this guess is, but it appears consistent with subsequent estimates. If anything, it may be too high.

Three centuries later, in 1950, the population of the world numbered about 2.4 billion, representing a four-fold increase since 1650. As a result of this acceleration in the rate of growth, the number of persons added to the population of the world during the past 100 years exceeds the total accumulated during the entire previous history of the human race.

There is ample statistical evidence that this increase resulted solely from a decrease in mortality rates and in spite of a sharp decline in the birth rate of the population of western Europe and North America, which was well under way as early as the first half of the nineteenth century. Around 1700, the expectation of life, at birth, of the population of North America and western Europe was about 33 years and probably had increased very little during the previous three or four centuries.[8] In 1948, the expectation of life, at birth, of the white population of the United States was 68 years, an increase of more than 100 per cent.[9] How was this dramatic reduction in mortality achieved?

Four factors were primarily responsible for man's increasing control over his environment: (a) the opening up of new continents, which provided additional sources of food, precious metals and other commodities as well as an outlet for surplus population; (b) the expansion of commerce, which made possible the transportation of food and capital goods over long distances; (c) technological changes in agriculture, together with the development of modern industrial processes; and (d) increased control of disease through improved housing, better food and water supplies, adoption of sanitary measures, the growth of the knowledge of preventive medicine and, more recently, discoveries in pharmacology and chemotherapy, particularly the antibiotic agents and newer insecticides.

These factors upset the near balance between fertility and mortality which had existed throughout the history of the human race with the consequent multiplication of population described above. Fortunately, before this increase became great enough to restore the former biological balance by again raising mortality until it checked fertility, the people of western European origin developed a new restraint upon uncontrolled fertility, contraception, or as it is more commonly called, birth control. This made possible the maintenance of a stationary or slowly increasing population by means of a low birth rate and a low death rate. To be sure, various peoples in the past have tried to control fertility by sexual taboos, postponement of marriage, abortion and infanticide, but never before had such large masses of population so effectively controlled their fertility.

The demographic revolution described above, however, has been participated in by only about one-third of the people of the world. Today, nearly two-thirds of the world's population has an estimated birth rate of 40 or more per 1,000 per year.[11] Included in this group are the people of Africa, Latin America and Asia, excepting the Japanese. Moreover, the people of Africa and Asia, except for the Japanese, still have death rates as high as those of western Europe two hundred years ago.

It is possible for these death rates to be reduced from a level of 30 to 35 per 1,000 to a level of 20 or below. The historic scourges of typhus, smallpox, plague, cholera and the enteric diseases can now be eliminated or controlled. Methods for curbing the great debilitating diseases, such as malaria, hookworm infestation, and other parasitic infections, are now well known.

It will be instructive to examine the demographic consequences of the application of modern public health knowledge in areas where fertility is near the biological maximum.

In 1940, Ceylon had a population of nearly six million and its birth rate was around 36 per 1,000 per year; its death rate had fallen to 21 per 1,000, high by western standards, but about one-third less than that of most Asiatic countries. In 1936, due to an outbreak of malaria, the death rate had risen to 37 per 1,000, slightly exceeding the birth rate. As late as 1946, the death rate still was above 20 per 1,000. Modern public health measures for the control of malaria and similar diseases were instituted. In 1947, the death rate per 1,000 was 14.3; in 1948, it was 13.2; and, in 1949, it fell to 12.6, a reduction of 40 per cent in three years. As a consequence, the crude rate of natural increase nearly doubled, rising from 14.7 in 1945 to 27.3 in 1949. At this rate, the population of Ceylon would double in 26 years.

Immediately prior to World War II, Japan had reduced her death rate to about 17 per 1,000, while her birth rate still remained in the neighborhood of 30 per 1,000. As a result of the disorganization of health and medical services, reduction in the food supply, and destruction of housing during the war, the death rate rose to 29.2 per 1,000 in 1945. Following the occupation by the Allied Forces at the end of 1945, vigorous public health measures were put into effect. These, combined with an improved food supply, reduced the death rate to 17.6 per 1,000 in 1947, and to a hitherto-unheard-of level, for an Asiatic nation, of 11.6 per 1,000 in 1949. This compares favorably with the death rate of 9.7 per 1,000 in the United States for the same year.

In the meantime, the birth rate increased rapidly, reaching a level of 34 per 1,000 in 1947, exceeding the pre-war rate of 30. During 1949, 1.8 million persons were added to the Japanese population of 80.1 million, due to natural increase alone. If continued, this rate of growth would double the Japanese population in 32 years.

When Puerto Rico was ceded by Spain to the United States in 1898, the Puerto Rican birth rate was above 40 per 1,000 and the death rate was between 25 and 30 per 1,000. During the first 30 years under United States rule, the birth rate remained at the high level of 40 per 1,000. The death rate declined slowly, but in 1932 was still 22 per 1,000.[12] At that time, the United States began to expend American relief funds in relatively large amounts, averaging fifty million dollars per year for the ensuing decade, an amount approximately equal to the total budget of the insular government.[13] As a consequence, the drop in the death rate was accelerated. In 1940, it had reached 18.4 per 1,000 and by 1948, 12.0 per 1,000. Meanwhile, the birth rate continued at the high level of 40 per 1,000. The inexorable demographic consequence has been a rapid multiplication of people on an already-overcrowded island. Partial relief has been found by emigration to the continental United States. In spite of this, however, the population grew from 1,544,000 in 1930 to 2,205,000 in 1950, an increase of 43 per cent in twenty years. The present excess of births over deaths is about 62,000 per year. If continued, this rate of natural increase would double the population of Puerto Rico in about 25 years.

These illustrations dramatically demonstrate the possible achievements in the reduction of high mortality rates, within a very brief period, by the widespread application of known public health measures. They also show clearly the demographic consequences of a simultaneous high birth rate and low death rate and the incompatibility of this relationship with the maintenance of a standard of living similar to that enjoyed by people of western European origin.

As can be seen from TABLE 2, a rapid decline in high-level mortality rates tends to increase the number of births, even with no change in fertility rates, due to an increase in the proportion of females surviving to the end of the child-bearing periods. In the United States, nine out of ten new-born white females can expect to live to the age of 50 years, the end of the child-bearing period. In India, the corresponding proportion is two out of ten.

Those who believe that the remaining two-thirds of the population of the world, who have not yet passed through the demographic revolution from high fertility and mortality rates to low fertility and mortality rates, can repeat the history of the western European peoples, neglect the following considerations.

The last great frontier of the world is closed. There remain no empty spaces comparable in area or wealth to those open in 1500 to the people of western European origin. Although there are vast thinly-populated areas in the world, their very existence is testimony to the fact that, until now, for one reason or another, these have been regarded as undesirable living places. The present population of the world is very unevenly distributed, about three-fourths of it living on one-seventh of the land area.[14] The four principal areas of population concentration are Europe; India and Pakistan; the Far East, including China, Manchuria and Japan; and eastern North America. This distribution represents an adjustment of population to natural resources which has been worked out over thousands of years. The expansion of population to the remaining open areas will involve extensive capital expenditures for irrigation, drainage, clearing of jungle vegetation, transportation facilities and control of insects and parasites; so that settlement by individual effort, which characterized so much of the early occupation of the Americas, Australia and New Zealand, is no longer practicable.

TABLE 2

PERCENTAGE OF NEW-BORN FEMALE INFANTS EXPECTED TO SURVIVE UNTIL SPECIFIED AGES BASED ON LIFE TABLES OF INDIA AND THE UNITED STATES

Age	*India*, 1921–31*	*United States†, white, 1948*
1	77	97
5	63	97
20	53	96
50	21	90
60	13	82
80	2	37

* Demographic Yearbook, 1948, United Nations.
† Vital Statistics of the United States, 1948, Part I, U. S. Public Health Service.

There are few opportunities even for a temporary relief of population pressure by migration. Probably 60 million persons migrated from Europe between 1820 and 1930.[15] The day of free migration is over, however; barriers to unrestricted movement exist in almost every nation. Even if this were not true, the number of potential migrants is so large, relative to the available space, that except in special instances, migration cannot be considered a practical means of relieving the pressures generated by rapid population growth.

The horn of plenty, filled with free natural resources, has been emptied. The rapid accumulation of capital in the form of precious metals, goods and commodities, so characteristic of the great boom of the past 400 years enjoyed by the peoples of western European origin, is no longer possible. Areas of known natural resources have already been occupied or seized.

Last, but not least, is the sheer arithmetic of the present population of the world. The number of persons now living on the face of the earth is so large that even small rates of natural increase will result in an almost astronomical increment over periods of time of infinitesimal duration compared with the past history of the human race. Between 1920 and 1950, the population of the world is estimated to have increased at a rate of about 0.9 per cent per year. Only during the decade of the 1930's has the crude rate of natural increase of the United States been as low as that. Yet a continuation of even this rate of increase would result in a world population of 14.3 billion in two centuries and 35.4 billion in three centuries or roughly the period of time which has elapsed since the Pilgrims landed on Plymouth Rock. Populations of this magnitude are so foreign to our experience that it is almost impossible to comprehend their significance. With a population of 35.4 billion, however, a uniform distribution over the entire land surface of the earth would allow each person an area one-eighth of a mile square. It seems very unlikely that the biological laws governing the adaptation of living organisms to their environment will permit an increase of this magnitude.

Just as Thomas Malthus, at the end of the eighteenth century, could not foresee the effect upon the peoples of western Europe of the exploitation of the last great frontier of the earth, so we today can no more clearly foresee the effect of the closing of this frontier. What seems least uncertain, in a future full of uncertainty, is that the demographic history of the next 400 years will not be similar to that of the past four centuries. The primary demographic question facing us today is, "How can the advantages of public health and medicine, now enjoyed by a minority of the world's people, be made available to all and at the same time keep fertility and mortality in close enough balance so that the benefits made possible by the control of mortality are not nullified by a rapid increase in population?" Man has been able to modify or control many natural phenomena, but no one has yet discovered how to evade the consequences of biological laws. No species has ever been able to multiply without limit. There are two biological checks upon rapid increase in numbers, a high mortality or a low fertility. Unlike other biological organisms, man can choose which of these checks shall be applied; but it must be one of them. The choice cannot be avoided.

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SOCIAL AND BIOLOGICAL FACTORS IN HUMAN FERTILITY

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Since 1850, the span of life for the average individual has increased in an unprecedented manner in many parts of the world. At the same time, new knowledge of sex physiology has made possible voluntary spacing of births, also a novel situation. These two manipulations of vital processes, achieved within the past century, constitute one of the great turning points in the history of our human race, comparable to the invention of the wheel and the alphabet or the development of agriculture. It is no exaggeration to call this perplexing century, in which our lives are cast, the beginning of the vital age.

If a man from Mars happened to visit this planet, he would surely be perplexed by several aspects of the population crisis reviewed by Doctors Thompson and Dorn.

An area of rather acrimonious discussion is provided by the relationship of people and provender. In the past century, there has been a vast increase in the human population of the earth. There has also been an unprecedented drain on many irreplaceable resources such as petroleum and iron, and upon the renewable resources, such as soil, forests and water. The depletion of these and many other resources has been widespread and shockingly wasteful. Stockpiles of minerals, considered inexhaustible a few years ago, have been depleted to the vanishing point in two generations.[1] In the shadow of growing scarcities, we are inclined to boast about this ruthless and reckless plundering of a planet. Those with the temerity to question the effects of exploitation are often attacked as "prophets of doom."

An advertisement currently being spread across the pages of national magazines by the Iron and Steel Institute is typical: "When you studied geography, did your book tell about the 'inexhaustible' store of high grade ore in the Mesabi Range of Minnesota? Millions of tons are still there, but we now know that this store of ore is not 'inexhaustible.' The enormous growth of the steel companies of America has forced them to develop new iron mines thousands of miles from home." New ore fields in the wilderness of northern Quebec, in Venezuela and Liberia, are touted as the modern Mesabis, "inexhaustible" in extent.

There is no immediate danger that the human race will run out of iron. Low grade ores exist in many lands, exceeding in potential the far-flung Mesabis now called upon to slake the iron-hunger of two billion humans. The cost of extraction, however, rises inexorably as the baser ores come into use. Our visitor from Mars would discover that the question of how these dwindling and ever-more-costly supplies of essential commodities are to be distributed among an ever-increasing number of human beings is one that hardly any of the people of the world are willing to contemplate, except through rose-colored spectacles.

A more sinister situation, the exploitation of the soil, also confronts the human species. Over large areas of the world today, the arable land of our planet is being mined, rather than conserved, or enhanced in fertility.[2] No country on earth today can boast that its soil is on a sustained-yield basis. That soil depletion and soil destruction is less serious in some parts of the world hardly justifies any lyrical optimism. There are today only about two acres of arable soil available to sustain each human being.[3] This is enough soil to enable all of us to eat fairly well if fertility is maintained. This is not being done and as a consequence, the twenty five million additional human beings each year who must be fed have a narrower margin of subsistence than the margin of the previous year.

There is no present prospect of any other source of bread than this exploited and eroding topsoil. There is a great reluctance to accept this fact, and to proceed to an appraisal of the possibilities. Instead, we are told that yeast, algae or pills, of some kind, will be forthcoming to nourish any multitude. If there are six human beings living today on such a synthetic diet I would be astonished. The myth of the synthetic diet, derived from "inexhaustible" raw materials produced independently of the soil, is not as harmless an illusion as it might seem. By keeping humans from taking seriously the grim game of "truth or consequences" in which we are engaged, the myth of the synthetic diet baits the trap for disaster.

This game of make-believe is played by many people in a great variety of contexts. In the city of New York last September, the International Congress of Pure and Applied Chemistry attracted nationwide notice in the daily press by staging a frontal attack on the "pessimists" who are so wrong-headed that they believe that a population problem exists.[4] The flying phalanx which attacked this "pessimism" was made up of six Nobel prizemen in chemistry. The keynoter was Artturo Virtanen of Finland, an agricultural biochemist. Virtanen said, "The world food supply could be increased enormously with the knowledge now on hand. No new discoveries are needed. If we could apply what we now know, we could produce enough food for four billion."

At the same meeting, President Conant of Harvard gazed into what he termed a plastic crystal ball, which he hoped would enable chemists to see into the future farther and better than a side-show seer. Conant saw that World War III would not be fought. "In 1985," he predicted, "biochemistry . . . has become the recognized successor of what was once called biology. . . . The use of new techniques has made the world food situation in 1999 something quite different from what it was fifty years before." He saw "harmless anti-fertility components" which fifty years hence would begin to slow down population growth. "The problem, while not solved, promises to be in hand before 2050."[5] The clear implication is that science has things under control and that we can relax.

On the occasion of the Massachusetts Institute of Technology Mid-Century Convocation in 1950, the technologists repeated, with variations, the refrain that science had everything under control. Vannevar Bush, Chairman of the wartime Office of Scientific Research and Development and

Director of the Carnegie Institution of Washington saw everything seesawing to a happy outcome.[6]

"Neither population nor science increases in geometric fashion indefinitely. When a lid is removed, they both start a burst of exponential growth, but science gets there first. As time goes on, they both level off until a new great opportunity opens. . . . Advances in tropical medicine now permit great additions to the total world food stock by opening vast areas to cultivation and by raising the work capabilities of the inhabitants. This will unquestionably also foster great population increase in that part of the world. But it is important to note that the opportunity for increases in the standards of living comes first. It is important because when the next pause comes it will be at a high level."

The chorus was re-echoed from England. On September 16, Lord John Boyd-Orr, first director of the Food and Agriculture Organization, was quoted as follows:[7]

"It is untrue that the [population] problem cannot be solved. It is perfectly possible for food to be produced at a faster rate than births. . . . If all nations were willing to cooperate in a great scheme of this kind [the 1946 FAO plan to double food production in 25 years] the world would be well on the way to abolishing hunger and poverty."

What conclusion could the man from Mars derive from such statements, made by persons of eminence in science or government? It should astonish no one that the public is misled to conclude by such blithe flights into fantasy that there is nothing to worry about. An editorial in the *Washington Star*[8] is a typical example of the illusions engendered by such statements.

"In [Dr. Virtanen's] judgment—and it is a judgment backed by equally distinguished scientists—the application of present agricultural knowledge throughout the world is all that is needed to raise enough high-quality food to provide excellent diets for a population of 4 billion. As he sees it, production today is not anywhere near what it can be in most countries. For example, the United States, if it wanted to, could greatly increase its yield of wheat per acre—a yield that is far below that of such lands as Denmark and only about a third of what he himself gets out of his own Finnish farm. As for the backward regions, they have only to learn modern techniques and achieve relatively minor technological improvements to reap much bigger harvests.

"This reassuring view, moreover, is based simply on *today's* agricultural knowledge—on what can be done right now with instruments and techniques that are already available. In talking about the world's ability to feed 4 billion people, Dr. Virtanen has purposely left out what science promises to achieve in the years ahead. That promise is very great in its potentialities. It includes the possibility of employing growth-regulating compounds to bring about a spectacular increase in the earth's crop yield and to make arid areas abundant in productivity. It includes also the possibility of a new type of chemical farming capable of producing vast quantities of sugars, starches and other vital foodstuffs. Above all, it includes the possibility that the harnessed atom will open man's eyes to the secret of photosynthesis and thus give him the key to a limitless food supply, no matter how fast his numbers multiply.

"Accordingly, if the peoples of the world do what Dr. Virtanen says they can do with the knowledge now at hand, and if science continues to move forward with its present highly promising experiments, there should be food enough for all, whether the number is 4 billion or even considerably more. In predicting a nightmare of starvation, the Cassandras seem very definitely to be grossly mistaken, as they so often are in so many other fields of human endeavor."

Under the circumstances, neither the newspapers nor the general public are to be blamed if they take these august assurances that a global miracle of the loaves and fishes is just around the corner. If it is literally true that the chemists can pull an infinite number of fat rabbits, or balanced-ration pills for that matter, out of their hats, then those of us who are frightened by the reckless destruction of the abundance of the planet Earth are indeed foolish Cassandras and feckless "prophets of doom." Is it irrelevant, however, to point out that, as of now, glowing promises of an inexhaustible horn of plenty have not filled one empty stomach among the more than one billion humans who today do not get enough to eat? Before the possibility of mass starvation is dismissed as a "nightmare," would it not be justifiable to ask the miracle boys to put on the line the basic food essential for this army of the hungry and near-naked? When that has been done, the boast that we can feed any multitude the biological process can bring into being a less hollow ring.

The truth is, of course, that the cornucopia boys do not really promise anything. The trouble with their pronouncements is that there is an "if" in every one of them: if the peoples of this world will cooperate without rancor and without the formidable drag of tradition, taboo, and cultural-economic blockages; if extant biochemical knowledge could be put to work tomorrow on every one of the half-billion farms which produce tomorrow's food; if tropical soil would not pack, leach and oxidize, so that ground-nuts might float the British Isles in a sea of peanut oil; then all might sit at a groaning board. The trouble is that a vast gulf separates the wishes of men and the realities of human existence, without ifs and buts. Through all of recorded history, it is this barrier that has kept beggars from having a coach-and-four or a Cadillac complete with chauffeur.

The reckless *if* and the large vague generality are hardly novelties. Commenting a century and a half ago on Abbe Raynal's dictum that the right to subsistence existed before social law, a champion of "what is" had this to say regarding another cornucopia pronouncement: "He [The Abbe Raynal] might with just as much propriety have said that before the institution of social laws every man had a right to live a hundred years. Undoubtedly he had then and has still a good right to live a hundred years, nay a thousand *if he can*, without interfering with the right of others to live; but the affair in both cases is principally an affair of power, not of right. Social laws very greatly increase this power, by enabling a much greater number to subsist than could subsist without them, and so far very greatly enlarge the right to subsist; but neither before nor after the institution of social laws could an unlimited number subsist; and before as well as since, he who ceased to have the power ceased to have the right."

The man who so eloquently doubted that the right to subsist will fill many empty stomachs was Curate Thomas Robert Malthus.[9]

Coming down out of the rosy clouds and taking a look at the world around us, what do we find?

In spite of all of our vaunted modern technical know-how, world production of food is not noticeably increasing. During the 1940's, World War II caused a marked decline in food production. It took several years after the shooting stopped before world food production approached the 1940 level.* Should FAO reach its goal of doubling world food production by 1976, there is every prospect that there will be enough people on hand so that none of it need go to waste. There is every prospect that by 1976 a quarter of a billion more people will need to be fed. To double the world's food production in a generation would be well-nigh miraculous. If it could be done, would a second doubling be possible in the succeeding generation? One industrial chemist whose view of the prospects is not colored by make-believe, made this comment on Lord Orr's statement: "It takes a good deal longer than nine months to gestate a technological revolution." Perhaps when the biochemists supplant biology and nature's method of making babies gives way to factory reproduction, this problem will be solved. Considering the hullabaloo which is raised when one suggests that modern fertility control has separated the two functions of sex, the emotional and the reproductive, this innovation will take a lot of selling.

The foregoing exploration of some of the perplexities and paradoxes of the population question has more relevance to the question of social and biological factors in human fertility than might casually seem to be the case. The question of achieving a rational and humane control of human fertility is central in averting the tragedy invited by the flights into the never-never lands and if-worlds which the cornucopia boys keep on offering as a "solution" to this urgent problem. It becomes a matter of crucial importance, therefore, to learn what makes people of great intelligence, unquestioned integrity and good will, so eager to play this dangerous game.

My impatience with pundits of science who beg the population question by promising miracles of loaves, fishes and/or algae does not imply that I underestimate the contribution that science might, and can, make to a solution of the problem. My objection stems from a fervent conviction that when science pretends to ape the vaudeville magician, it ceases to be science. Ability to mass-produce food does not free human beings from the urgent responsibility of considering the optimum population of the world, and preventing hopeless multiplication beyond this optimum, in a mad scramble of breeding. If this aspect of the matter is ignored, it is a biological possibility that, within a couple of centuries, if the chemists will foot the bill, we will fill up the entire land area of the planet with people, as closely packed as they are today on Manhattan Island.

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* The 1950–51 report of FAO states that, by 1951, world food production had increased 9 per cent over the 1934–38 average; world population has increased 12 per cent in the same interval.

When leaders in government, science and the learned professions approach the population problem with a sophistication expected of a kindergarten class, there must be a reason. Is this strange inability to do simple sums in vital arithmetic to be ascribed to a biological deficiency in their makeup? Should it be ascribed to environment rather than to heredity?

It is my conviction that both biological nature and social nurture contribute to this strange behavior. That area of the human personality which is centered around sex drives and sex behavior has been identified by Sigmund Freud as a mental and emotional storm center of the human psyche. Even though one may find it hard to follow some of the wilder flights of psychoanalytic fancy, there is no question that the tensions built up by the conflict between instinctive and physiological sexual drives, on the one hand, and moral-social inhibitions and taboos, on the other, are a potent source of confusion, conflict and irrational behavior in many, perhaps in most, human cultures.

The portentous question of human fertility must be approached against this background in its personal and in its broader social, political and ethical aspects. In Western cultures, especially during the past century, there has been a profound conflict between the "facts of life," the realities of sex physiology and psychology, on the one hand, and, on the other, the traditional sex behavior patterns, and attitudes regarding sex, which are deeply rooted in the culture in which we live. This entire area is rife with unacknowledged conflicts and frustrations.

Such tensions are not new. For ages, man has found sex to be a subject fraught with joy and sorrow, perplexity, stress and confusion. The need to control fertility, so that excessive numbers will not swamp a precariously-balanced economy, has been recognized for ages. Human cultures have elaborated an astonishing variety of customs, social imperatives and religious taboos to keep fertility within bounds. The taboo against sexual intercourse during lactation (and the longer the lactation the better) is a case in point. The "churching" rite of the Anglican Church is no doubt a vestigial fertility-control custom. The celibacy of the clergy is another. When such indirect means of fertility failed, recourse was often had to direct action, abortion and infanticide. Even today, these expedients are employed more often than we like to admit.

The other face of the coin of life and death contributed its quota to the confusion. Mortality has been so high, during infancy and childhood, since man took up residence on this planet, that any tribe or clan which did not maintain a safe margin of excess fertility was in danger of extinction. Any tribe or nation which showed any marked ability to take sex or leave it alone was, *ipso facto*, on the way out. As a rule, there was no need to resort to abortion and infanticide. Wars, epidemics and famines have placed an urgent emphasis upon fertility as being essential for survival. This has given rise to the persistent obsession that unlimited fertility, in itself, is a blessing, a point of view which all too frequently colors some very august pronouncements regarding population. Even in pathetically overcrowded corners of the earth, a gain in population is universally called "favorable" in demographic discussions. A decline in numbers, even when such a decline might prevent deaths by famine, is viewed as a disaster.

In the United States, only 2.2 children per woman are needed to maintain a balance in numbers. Nevertheless, physicians and clergymen, and now and then a government agency* assures us that unless the proportion of families having four to six children increases considerably, extinction is just around the corner. What would happen in the United States if we suddenly began to follow eighteenth century fertility patterns never bothers such people. The average woman bore at least eight children in that era. With current rates of natural increase this would mean a rocketing of numbers, more than doubling the population in each generation.

Thus, in every culture, the population problem presents assorted paradoxes and conflicts. Along with a reluctant recognition of the need to control fertility, there is an acute interest, often obsessive in its manifestations, in the phenomena of conception, gestation and birth. Every religion has a strong tincture of fertility cultism in many of its rituals. Customs, superstitions, and rituals centering around the phenomena of conception and birth are among the most deep-rooted and persistent vestiges of an ancient social heritage. One wonders whether they do not have a biological, rather than a mere cultural basis. In the past, as we have seen, this preoccupation with fertility had survival value.

A recent book by Albert Ellis, by an analysis of current sex behavior, overt and verbal, attempts to explore this deep-seated confusion which today so gravely threatens the future welfare of the entire human race. Ellis points out that, superficially, the official and legal views regarding sex in the United States appear to be well-crystallized, but that this is only the mask that conceals a deep-seated turmoil. Beneath the surface, the true picture of the proverbially "average American," says he, "should be that of an individual whose sex attitudes are woefully addled, twaddled and straddled."

The ability to prolong life and to make birth a matter of volition rather than a too-often calamitous by-product of the passion between the sexes has resulted, in the first century of the vital age, in the quagmire of confusion sketched above.

That this is true seems to me to be the key to the confusion which today marks many discussions of the population question. The addled, twaddled and straddled pronouncements regarding the nature of the population crisis and the steps which must be taken to meet it would certainly cause a visitor from Mars to wonder whether the intelligence of the human species has been vastly overrated.†

That humankind is in grave danger of becoming trapped in a rising cycle of misery and despair because of this mare's nest of compounded confusions is tragic indeed. The trouble cannot be solved by eliminating biology, either at the level of agricultural production or human reproduction. It is essential that policy makers and builders of public opinion recognize this conflict between old imperatives and new powers, with their ancillary responsibilities. A psychiatrist of distinction put his finger some years ago on the cultural aspects of this surpassing problem in these words: "Misguided by authoritarian dogma, bound by exclusive faith, stunted by inculcated loyalty, torn by frantic heresy, bedevilled by insistent schism, drugged by ecstatic experience, confused by conflicting certainty, bewildered by invented mystery, and loaded down by the weight of guilt and fear engendered by its own original promise, the unfortunate human race, deprived by these incubi of its only defences and its only reasons for striving, its reasoning power and its natural capacity to enjoy the satisfaction of its natural urges, struggles along under its ghastly self-imposed burden. The results, the inevitable results, are frustration, inferiority, neurosis and inability to enjoy living, to reason clearly or to make a world fit to live in."[13]

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* As an example of this, it is interesting to refer to the official announcement of the U. S. Census Bureau on February 7, 1939, stating that the "U. S. population is declining." What the statistics showed was that if births and deaths followed certain trends for nearly a generation, the population would stabilize in numbers and would eventually begin a slow decline. Even at the time the announcement was made, rising birth rates indicated that a stabilization of U. S. population was not imminent. Today, the U. S. rate of natural increase is such that stabilization appears to be several generations in the future.

† Since the above was written I have been privileged to read Professor Flugel's searching analysis[14] of the hidden psychological barriers to an acceptance of the Malthusian axiom that population persistently presses upon resources. This discussion does much to make clear the dynamics of the hidden rationalizations which impel Dr. Bush (an American), Sir Boyd-Orr (a Briton), Dr. Virtanen (a Finn), and Eugenio Pacelli (an Italian), to insist in different jargons and in most varied contexts that "God never sends mouths but He sends food."

The frustration, the neuroses and the hair-shirt of guilt and perplexity contribute significantly to the world's net gain of some 70,000 human beings each day. It is surely a hopeful sign that the author of this plea to break the shackles of the past, Dr. Brock Chisholm, is now Director of the World Health Organization.

What has happened in the past century has made possible a new purpose and has given a new dignity to the epic cycle of human birth, growth, and death. Potentially, the divorce of the physical attraction between the sexes from the purpose of procreation represents a great release and a great challenge. It marks a new, most exciting, and portentous step forward in the evolution of human interpersonal relations. If people could only glimpse what it might mean to tomorrow's children and adults, if only wanted babies were born in the future, think what kind of a world this might be within a century. It might be indeed a world fit to live in! So great is the confusion in current thinking about this matter, that what is in reality a historic milestone in the evolutionary process has been mistaken for a gravestone by all too many of our leaders.

That the functions of our bodies acquire purposes different from those for which they were originally adapted is a commonplace in the story of evolution. The progenitors of the birds we know had feathers to keep them warm. At another stage of evolutionary emergence, wings were used for flight.

In terms of the original use, this new use was no doubt "unnatural." This new utilization, however, marked an important evolutionary step to a higher level of differentiation and specialization. By learning how to defer early death and make conception voluntary, humankind, whether it likes it or not, has behaved in a most "unnatural" manner, in boldly undertaking the direction of its own evolution. Whether this fact is recognized by humankind does not alter in the least the fact that man's social and political acts now increasingly determine his evolutionary fate.

The important point is that a recognition of this situation may determine the future direction of evolution. Evolution by default will inevitably lead to a decline in the fitness, mental and physical, of human beings. The selection process which has determined the direction of evolution in the past operated by the death-veto of variants which were unable to fit into the existing environment for many different reasons. Under those conditions, a reckless spawning had evolutionary value by exposing a great array of variant types to the screening of unremitting death selection.

In this process, the ill-adapted variants, including many pathological hereditary defects, were kept at a low frequency. Without selection against ill-adapted variants, biological fitness must inevitably decline, and rather rapidly. The recent analysis of this situation by Professor George Beadle of the California Institute of Technology[15] leaves little basis for a smug attitude that we can, merely by refusing to consider what effects changing birth and death rates will have, escape the consequences of our acts. Mere Christian kindliness and vague good intentions cannot of themselves save either the cultural or biological bacon of our human race.

It is very important to bear the following fact in mind: selection can be accomplished by birth as well as by death. In the present context, it is more than a possibility that the direction of human evolution in the future will depend not so much on the many who die, as it depends on the fewer who are born. When the vast majority of a population survives beyond the reproductive years, death tends to lose some of its significance as a selective force. As death selection becomes ineffective, the quality of babies born (in terms of mental and physical and moral fitness), will determine in proportion the direction of evolution, in so far as these fitnesses are genetic. The way the question, "Who shall be born?" is answered in the future by the people of the world will increasingly determine the fate of our human species on this earth.

If the biological and social factors in human fertility can be brought to bear effectively and humanely, to assure the fitness of tomorrow's children in every land, the future will offer excellent prospects of a good life for all.

It is a far cry from the present state of conflict and confusion to the moment when a rational approach to the population problem will be possible. But there does seem to be an awakening. The government of India, in recent months, has recognized that control of numbers is the crux of India's problem and action is following fast on this realization. India's appeal to the World Health Organization for help has brought the quick dispatch of a Commission to survey the situation and to recommend measures to balance births and deaths.

Let us hope that this awakening is not too late. Let us hope that the Western World can provide weapons in this new sector of the fight for a good life as effective as the sulfas and the antibiotics and the DDT's in other sectors. Cheap, simple, effective and acceptable contraceptives really well-adapted to crowded conditions of living, have not yet been perfected. Even if the perfect contraceptive existed, the opposition to its wide-spread use would be enormous, for the barriers to acceptance of a rational approach to the problem of human fertility are high. There is not much prospect that a peaceful world and a good life for all can be realized until it is possible to achieve a control in numbers so that a rising standard of living for all may be attained. To break down these barriers is the great opportunity and the great challenge for the social inventor in this first century of the vital age.

That this conference has been called by the New York Academy of Sciences is most heartening evidence that the awakening is not limited to India. As far as I am aware, this is the first time an Academy of Sciences in the United States has undertaken to explore this problem in its broad sociological, physiological and medical aspects. It is indeed an honor to have the privilege of participation in this historic meeting. These encouraging developments in New Delhi and on the other side of the world in New York may indeed herald the dawn of a new day.

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DISCUSSION OF PAPERS BY DOCTORS THOMPSON, DORN, AND COOK

DOCTOR CLYDE V. KISER, *Milbank Memorial Fund, New York:* Being in substantial agreement with most of the views expressed in the three preceding papers, I find little with which I can take issue. I should like to underscore certain points, however, and mention one or two possible qualifications to the remarks made.

I consider that Dr. Thompson was right in emphasizing that it is better to think in terms of concrete problems existing in specific countries than in terms of one single type of population problem. It is well to remember that about 20 per cent of the world's population, *i.e.*, the inhabitants of the most modernized countries of the world (Western Europe, the United States, Canada, Australia, New Zealand) face the problem of maintaining their numbers rather than the problem of runaway fertility of their own people. It is true that most of these countries experienced substantial increases in birth rates during and after the last war. These increases, however, are believed by most demographers to be rather temporary. I doubt that there is any reason to discontinue labeling the demographic type of these countries as "stationary peoples," as Thompson has done in some of his writings, or as countries of "incipient decline," as Notestein has preferred to call them.

Another 20 per cent of the world's population is in countries demographically classified as those of "expanding peoples" by Thompson and of "transitional growth" by Notestein. These are the peoples of Eastern Europe, the U.S.S.R., Japan, one or two of the most advanced Latin American countries, Turkey, Israel, and parts of North Africa. In these countries, varying degrees of progress have been made in bringing fertility under control. The birth rates are falling but they are still sufficiently above the death rates to yield rapid population growth for at least another generation. Merely to list the names of countries in this category is to underscore another point made by Thompson, *i.e.*, the wide variety of economic and social conditions. Thus, the U.S.S.R., with her immense territory and resources, probably will have little difficulty in accommodating her prospective population increase, particularly if she turns her attention to internal development rather than to aggression. Japan, on the other hand, doubtless will have a difficult time, in view of her limited area and resources.

The remaining 60 per cent or so of the world's population has scarcely been affected by the demographic revolution from high to low mortality and fertility rates. The countries involved are those that we now call the underdeveloped areas: all of Asia, except Japan and the U.S.S.R., the islands of the Pacific and Caribbean, much of Latin America, and most of Central Africa. Their demographic type has been labeled as "pre-industrial" by Thompson and as "high growth potential" by Notestein. Their rates of growth have not been high in the past, because high birth rates have been largely offset by high death rates. A great "demographic dilemma" is inherent in the tendency for modernization to bring reductions in mortality before it brings reductions in fertility, and hence to be followed by a period of heavy population growth.

I think Dr. Dorn did well to take as a point of departure Walter Prescott Webb's article in the October, 1951, issue of Harpers Magazine, "Ended: 400 Year Boom, Reflections on the Age of the Frontier." The article is not directed primarily to the world population problem, but it emphasizes that the European peoples and their descendants fell heir to the great boom resulting from discoveries of new lands. The new lands had room to accommodate the heavy increase of European peoples that followed the modernizing effects of the Industrial Revolution and lasted until it was checked by increasing resort to contraception. The non-European peoples were not privileged to participate in this boom. Their period of prospective declines in mortality comes at a time when there are no new areas for settlement. As Dr. Dorn has stated, they must inevitably make an early choice between fertility control and death control.

When I first saw the title of Dr. Dorn's paper, I hoped that he would venture some assessment of the relative roles of public health and economic improvements in lowering death rates in the past. This, of course, is a very difficult question because the two types of improvement have tended to go together. It is of more than academic interest, however. We have the various types of specialized agencies, such as FAO and WHO, operating sometimes together and sometimes rather independently in the underdeveloped areas. For the past several years, as Dr. Dorn indicated, we have witnessed rather astounding declines in the death rate in places like Ceylon, presumably due almost entirely to simple wholesale spraying with DDT.

I found Dr. Cook's paper, like his recent book, *Human Fertility*, provocative in spots, but never dull. A substantial part of his paper is devoted to what has been called the "great debate" on the future resources and food supply in relation to population. It is interesting to note that the main participants in this debate have not been demographers but people in other fields. Perhaps, like Dr. Thompson, most of the students of population feel that the terms of reference in this debate usually have been too vague to be meaningful. Thus, when the "optimists" confidently predict that there will be enough food to support the increased population, we want to know for how long, at what level, and perhaps also, for what purpose.

Whereas the "optimists," however, seem to think at times simply in terms of feeding at the fruit-fly level, the "pessimists" in the case seem to think that human beings will reproduce everlastingly at the fruit-fly level. They sometimes fail to credit man with the capacity either to replenish some of his resources, or to learn eventually to control his fertility. Dr. Conrad Taeuber made a sober comment on this entire question of the prospective comparative trends in population and food production when he said, "It would be difficult to suggest a field in which there is more need for careful research and a greater temptation to generalize from inadequate information."[1]

Whatever the correct answer to that question may be, few will disagree with the proposition, emphasized at this session, that ways and means must be found to speed declines in fertility, as well as in mortality, if there is to be any permanent improvement in levels of living in the underdeveloped areas of dense settlement. The discouraging thing is that no one, including the demographers, can produce a prescription guaranteed to lower birth rates in agrarian societies. We have learned from experience, however, to recognize a few of the things which must be avoided. We have learned that the colonial type of development which traditionally has been directed toward increases in certain raw products, with a little health work on the side, almost universally results in declines in mortality and the persistence of high levels of fertility. It is an old maxim in sociology that it is fairly easy to induce a primitive to substitute a steel plow for a wooden plow, but it is difficult to get him to change his institutions of marriage, family, and religion. It is in these institutions, customs, mores, and values that the patterns of high fertility of agrarian areas are imbedded.

Pending further knowledge of ways and means of approaching the problem, we believe that certain principles should be observed. The will to reduce fertility must come from the people themselves. Until this comes, there is not much use in trying to spread the means of family limitation. Simple, cheap, and acceptable methods, however, should be made available as rapidly as possible and native people should be given assistance and encouragement in doing research of this type themselves. There is reason to believe that programs directed to the elevation of the status of women through improved educational and gainful employment opportunities might implant desires for smaller families.

To end on a faint note of optimism, we are encouraged to see that Nehru of India, perhaps as a result of the most recent famine, has acknowledged the need for reductions in family size among his hard-pressed peoples. In a recent article, Kingsley Davis ventured the prediction that Puerto Rico is on the brink of sharp declines in fertility.[2] Some basis for this point of view is also afforded by Paul Hatt's recently completed study of Puerto Rican fertility in relation to attitudes and cultural factors.[3] There are also signs of increasing interest in family limitation in other parts of the world.

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CONTROL OF CONCEPTION IN CROSS-CULTURAL PERSPECTIVE

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This paper attempts to block out in rough fashion the ways in which conception is controlled in a large number of different societies. The generalizations which follow were obtained by examining data on 200 societies from all over the world.

These peoples differ markedly from one another. They live in environments that range from tropic to arctic regions and from sea level to altitudes of more than 10,000 feet. Their customs and traditions are totally dissimilar. Their ways of life bear little resemblance to one another. They are all concerned, however, with the problems involved in the control of conception.

Attempts to Induce Conception. A particularly striking fact emerging from this survey is the universal concern over the inability of an adult woman to conceive. In nearly every one of these societies, the barren woman is either an object of pity or scorn, and occupies a position almost as inferior as that of the spinster. In nearly every one of these societies, moreover, recognized techniques or practices are available to help correct a woman's inability to conceive. Some of the methods are clearly magical and ineffective. They may allay anxiety and mitigate guilt, but otherwise they can only be understood in the light of native theories of conception.

Most peoples recognize that sexual intercourse is related to impregnation, but most of them believe that other factors must also be of considerable importance. Otherwise, why does conception follow some sex acts and not others? Clearly, this requires explanation. To solve this dilemma, many societies make recourse to the supernatural. Infertile sex acts occur because the Gods are not favorable. The way to counteract barrenness, therefore, is to cajole or coerce the Gods into a more favorable attitude. The explanation may be that women only conceive when there is an ancestor ready and waiting to be reborn.

A few examples will serve to illustrate these beliefs. Among the Abelam, it is thought that a woman is made pregnant through the activities of a water spirit while she is bathing and that coitus between husband and wife serves primarily to build up the fetus which has been fastened inside the vagina by the water spirit. The Dahomeans believe that all souls are provided by the sky god associated with the moon, and that deified ancestors supply the clay for new bodies which enter the womb of a woman in sexual intercourse. To them, conception cannot occur without both of these ingredients.

Other peoples, however, simply assume that one sex act is simply insufficient for conception and that several acts of intercourse are necessary before a woman can become pregnant. If prolonged intercourse does not result in conception, medicines are prescribed in the belief that her condition possibly can be remedied. A surprisingly large number of peoples conclude that a woman who has had regular intercourse over a period of time and fails to become pregnant is mismated. She is, therefore, expected to try another partner. She either marries another man or, more frequently, she takes a lover with her husband's consent. A few peoples accomplish comparable results by refusing to recognize a marriage until the couple have succeeded in demonstrating the fertility of their union.

It is of considerable interest that a few societies believe that sex acts are more likely to result in conception just after a woman has menstruated than at any other time. They are so convinced of this that at least one people, the Hopi Indians, base their method of contraception on it, and consider the period just before menstruation as a "safe time" for sexual intercourse.

Very few peoples seem to consider the possibility of the man's infertility. Impotence in the male is recognized and generally despised, but the question of a man's fertility rarely seems to be raised. Unless a man is impotent, lack of conception is inevitably blamed upon the woman or, at the very most, upon an infertile union.

The extreme concern over a woman's failure to bear children becomes even more impressive in view of the attention paid to her once she is believed to be pregnant. In most societies, she is forced, almost at once, to begin observing a myriad of restrictions and to follow traditional rules designed to insure the safe delivery of a healthy baby. She is expected to diet and follows a large number of specific dietary taboos. Generally speaking, fats and meats are reduced in quantity. In some societies, sweets are forbidden; in others, salt is taboo. Many peoples fear that the fetus will be too large if these restrictions are not followed. Less logical justifications, from a medical point of view, accompany many of these taboos. Intestines may not be eaten in some societies for fear that they may entangle the fetus. Whatever the justification, however, the net effect is reduction of the woman's total diet and, in particular, the amount of protein consumed. These restrictions serve to emphasize over and over again the woman's responsibility to do everything in her power to bring her child safely to term.

In addition to observing dietary restrictions, the pregnant woman is also expected, in most societies, to abstain from sexual intercourse. Some peoples insist upon this restriction early in pregnancy and nearly all insist upon it during the last month or two. The justification for this restriction is also in terms of the welfare of the mother and the fetus. In particular, fear of miscarriage is given as the reason for abstinence from coitus or, at least some modification of the normal coital pattern.

A series of miscellaneous rules, of one sort or another, supplement restrictions on the sexual behavior and diet of the pregnant woman. These vary in number and type from one society to another and the details need not concern us here. The major point to be made is that most societies seem to be greatly concerned over the welfare of the pregnant woman and her unborn child. Considering also the extreme pressures against childlessness, they express in eloquent fashion society's interest in reproduction, as viewed in cross-cultural perspective.

Attempts to Prevent Conception. We have noted that attempts to induce conception are linked to a number of other measures which are taken to insure the birth of healthy offspring. In the same way, attempts to prevent conception may be considered one way to avoid having children. Contraception is thus regarded, along with abortion and infanticide, as a method by which children can be avoided. From a practical point of view, contraception is the simplest way out, if an effective technique is known. Willful abortion carries with it certain dangers to the welfare of the pregnant woman. Infanticide can only take place after the period of pregnancy and the pain of childbirth have been endured. It is therefore likely that people, whenever they choose not to have offspring, will choose contraception, if they can avail themselves of an effective technique, in preference to aborting the fetus or killing the newly-born.

Viewed in cross-cultural perspective, both abortion and infanticide are universally known. In nearly every society, they are practiced at least occasionally. At the same time, it is also clear that strong social pressures are brought to bear against any excessive indulgence in abortion and infanticide. Most societies permit the riddance of a child under specially defined circumstances only. Abortions, for example, may be permitted if the mother is still nursing another, and infanticide may be customary in the case of multiple births. Generally, however, both abortion and infanticide come under rather strict social control.

It is probably of considerable significance that abortion is generally considered less seriously than infanticide by most societies. Furthermore infanticide is most readily condoned if it occurs before the infant is named and has been accepted as a *bona fide* member of its society. It seems that the primary and fundamental restriction in most societies is the taboo on murder, *i.e.*, killing a member of the ingroup. The less eligible a child is for membership in the group, the less seriously the act of killing the child is viewed. Support for this interpretation comes from the reasons advanced by many peoples for permitting and even urging infanticide under certain conditions. If a baby is born malformed and fails to conform to the cultural standards, he may be killed without negative sanction in many societies. Such a child is not eligible to membership in the group. Twins are killed in some societies if they are of opposite sex. It is assumed that they have committed incest within the womb and have thus forfeited their right to live.

If the view is correct that restrictions on infanticide and willful abortion are progressively weaker extensions of the taboo on ingroup murder, this may help to explain why taboos on contraception do not exist in most societies. Extending a taboo on murder to the destruction of a fetus before it is conceived is too great an extension for most people. Contraception is thus combatted in most societies only by the many inducements extended for fertility in women.

Contraceptive attempts are not, therefore, viewed as either sinful or criminal in most societies, and some sort of device to prevent conception is available to the members of practically all the societies in our sample. These techniques designed to prevent conception vary markedly in their probable effectiveness. Some are so clearly magical that they may be dismissed at once as having no practical effect. Others, just as clearly, are relatively effective mechanical devices that help to reduce the probability of conception. A few examples of these may be of interest. Inserting a pad of bark cloth or a rag in the vagina before intercourse is commonly practiced to prevent conception among some peoples in Oceania and Africa. Attempts to flush out the seminal fluid with water after intercourse is practiced by a few peoples scattered in various parts of the world.

A surprisingly large number of peoples apparently have drawn independent conclusions to the effect that conception can be avoided by taking some drug or medicine. Unfortunately, from the standpoint of testing the possible effectiveness of these concoctions, the literature rarely reveals the precise nature of the ingredients. For example, it is recorded that the natives of the Solomon Islands prepare a medicine from the bark of certain trees. The woman who takes this medicine is said to become barren for the rest of her life, and she usually takes it after she has had two or three children. For many societies, it is simply recorded that the women can render themselves sterile by chewing certain leaves. In a few instances, however, the plant from which the medicine is made is known. The Sanpoil boil the roots of dogbane (*Aposynum androsaenifolium*) and drink the concoction as a contraceptive. The Indian tribes of Nevada use *Lithosperma ruderale* (Boraginaceae) as a contraceptive, the women drinking an infusion from the roots for a period of six months. Preliminary experimental work showed that feeding mice with alcoholic extracts of this plant abolished the normal estrous cycle, and decreased the weights of the sex organs, thymus, and pituitary. Noble, Plunkett, and Taylor[1] carried on the research by administering lyophylized aqueous extracts of both the tops and roots of the plant to rats and found that the number of estrous smears decreased. Subsequent work with rabbits led them to conclude that *Lithosperma* apparently inhibits the actions of gonadotrophins on the ovary. In view of the original uses of the plant, the authors suggest that the unit of activity in *Lithosperma* be expressed in terms of P. P. U's, *i.e.*, Papoose Preventative Units.

The most effective means of contraception employed by these societies is that of abstinence from complete coitus. There are many taboos on sexual intercourse in human societies that cannot be classed as purposeful attempts to avoid conception,[2] but there are many circumstances under which the primary justification for avoiding intercourse is the prevention of pregnancy. It may be of interest to examine the conditions under which attempts to prevent conception by avoiding coitus are most commonly practiced.

It is extremely common in cross-cultural perspective to find a taboo on sexual intercourse during the period when the mother is nursing her newly-born child. The period may be as short as six months or as long as four or five years after childbirth. In nearly every instance, the justification for this abstinence is the prevention of conception. In some societies, this desire is coupled with the belief that the nature of the milk supply will radically change and production of milk may stop altogether if a nursing mother becomes pregnant. In others, the fear is simply that the consecutive appearance of another infant would jeopardize the life of the older child, since the mother might not have enough milk for both. Apparently, the practice in most of these societies is that abstinence continues for one or perhaps two years after childbirth and intercourse is then resumed, so that the nursing child is weaned at the age of two-and-one-half to three years, as soon as it is known that the mother is pregnant.

Other taboos on sexual intercourse, often justified in avoiding conception, are those which forbid the unmarried girl to enjoy this experience. This is not generally the case; a large number of the societies in our sample permit the unmarried girl to have intercourse. It is probably significant that relatively few girls become pregnant in the first few years after menarche, despite freedom to carry on love affairs. Forbidding intercourse for the unmarried girl, in those societies which insist upon it, is probably far more complicated than a simple attempt to prevent the birth of a child to an unmarried mother. On the other hand, there are a few societies, such as the Masai of Africa, who specifically insist on pseudo-intercourse of one kind or another before marriage. Premarital love affairs are accepted, in their view, and anything goes, except complete coitus, which might result in pregnancy.

Attempts to avoid children in these societies are not restricted to unmarried girls and nursing women. It is reported that the women in many societies are reluctant to bear children for a variety of reasons. Some fear the pain of childbirth, others resent the changes in their way of life imposed by pregnancy and motherhood, and still others fear that they will be unable to support a child, particularly if they are burdened already with two or three. In some societies, there are definite policies governing the number of children a family should have. Firth[3] quotes a source in Oceania, "Families by Tikopia custom are made corresponding to orchards in the woods. If children are produced in plenty, then they go and steal because their orchards are few. So families in our land are not made large in truth; they are made small. If the family groups are large and they go and steal, they eat from the orchards, and if this goes on they kill each other." On Nukuoro island, the native chief decides whether the child of a pregnant woman should be aborted or allowed to live. His decision rests upon considerations of public welfare, *i.e.*, whether the community can afford to support another member at this point. The Fiji Islanders believe that the ideal family consists of four children, born four years apart, and apparently they achieve remarkable accuracy.

Emerging from this brief survey of the control of conception in cross-cultural perspective is the impression of a delicate balance between pressures toward bearing children and tendencies to avoid birth. The evidence suggests that strong tendencies to avoid children are generated under the conditions of social life. The restrictions imposed upon the pregnant woman, habits that must be changed, fear of pain and death at childbirth, and the years of care demanded by the infant all tend to discourage the woman from bearing children. A strong maternal instinct may overcome these tendencies unaided, but such an instinct, if it is present in human beings at all, is patently too weak to combat the continuously-generated desire to avoid children. Instead, we find social pressures toward preg nancy, bringing the fetus safely through the period of pregnancy and parturition, and care of the baby during infancy. Women are taught from childhood that their mission in life, among others, is to bear children and to love them. Tendencies to avoid the responsibilities of motherhood are thus successfully combatted.

The practical import of this conclusion is obvious. We may assume that tendencies to avoid childbearing and its attendant discomforts and responsibilities will be generated in any society. We may assume further that these tendencies will be combatted (although unwittingly) by a whole matrix of social pressures which operate throughout the woman's lifetime. In other words, there are positive and negative attempts to control conception in every society, and these will be found in delicate balance with one another. Attempts to introduce new attitudes or procedures into a society will depend for their effectiveness upon the manner in which the society exercieses control over conception and childbearing.

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PRESENT-DAY INTERNATIONAL TRENDS IN FAMILY PLANNING

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Birth control is both old and new. As a social practice it is old; as a social movement it is new. It is old in the sense that contraceptive knowledge in some form, often mixed with magic, has existed for ages. It is new in the sense that the knowledge of contraception is gradually becoming democratized and that today we are able better to distinguish between the rational and irrational, harmless and harmful, reliable and unreliable methods.

Long before the dawn of written history, savage peoples made some attempts to adjust their populations to their food supplies. They did this by wasteful and cruel methods of infanticide, abortion, killing the aged, by ritual taboos on the time of intercourse, and by prolonging the nursing period. More effective in limiting population were the involuntary checks of disease, famine, floods, and wars. Only recently have scientific preventive measures been developed, and today they are beginning to play an important role in family and population planning.

The growing interest the world over in planned parenthood stems from the medical awareness that family planning and child spacing are necessary for the physical well-being of mother and child; from the psychological awareness that the removal of fear and anxiety of an unwanted conception is necessary for the emotional stability of the home and family life; from a spiritual conviction that voluntary parenthood, the conscious control of reproduction, contributes to human dignity and the ethical values of life; and from our growing social awareness that a better balance between populations and resources, between human fertility and soil fertility, is essential for the welfare of nations and the peace of the world.

Today, we are faced with two major global phenomena: The fertility of man is increasing at a rate faster than ever before in the history of the world and, at the same time, the fertility of the soil is rapidly declining. The curve of population growth is ascending steeply, while that of the world's resources is descending. Nearly two-thirds of the world population, approximately two out of every three of the men, women and children on the face of the earth, are without the basic necessities of life. Millions of people are living at a mere subsistence level, and are constantly faced with actual starvation.

In an address before a conference of Unesco on April 15, 1950, Jaime Rorres Bodet, the director general, stated that the question of food and people was "the gravest international problem today from the long-term standpoint."

"The world's population is increasing in excess of 20,000,000 a year," Mr. Bodet said. "These millions must be fed. Yet we are not producing enough food for our present population. Even before World War II some two-thirds of the world's people were not getting enough to eat. Unless food production is brought into balance with population increases, humanity faces an unprecedented catastrophe." This is a sober statement and obviously requires the serious consideration of social and biological scientists everywhere.

How can this major human problem be met? Where lies the solution to this great human dilemma? Clearly, it can be approached from two sides. Global steps must be taken to preserve and restore our soil and waters, increase food production the world over by modern and improved agricultural methods, and develop new sources of nutrition though new research and exploration. At the same time, however, national and international measures must be developed to stabilize human fertility, to bring into better balance the number of people and the resources of the world.

What is being done in the world today as far as population planning is concerned? Let me briefly review the present status of planned parenthood in the various major countries of the world on the basis of many personal observations in recent years and reports which have come to the International Committee on Planned Parenthood.

1. *England.* Malthusianism originated in England, and Great Britain was one of the first countries to accept family planning as a social practice. Planned Parenthood clinics have been in existence in England for more than a quarter of a century, and the English Family Planning Association has functioned as an active and effective organization for many years. Special attention was directed to the problems of voluntary parenthood and population planning recently in the official report of the Royal Commission on Population. This Commission was appointed in England in 1944 to examine the facts relating to the population trends in Great Britain and to consider what measures, if any, should be taken in the national interests to influence the future trend of population. The Commission made an extensive and highly competent survey of the situation, and its report and recommendations were published in 1949. On the question of voluntary parenthood, the Report says: "We take the view that it is in the long run interests of the family that voluntary parenthood should become universal and that women should have the maximum freedom in the ordering of their lives. We believe that the instinctive desire for a family and the realization of its lasting satisfactions may be relied upon, given reasonable social conditions, to ensure that families will be of sufficient size to replace the population from one generation to another. The problem is to create those social conditions on the assumption of a further spread of the practice of deliberate family limitation.

"We contemplate therefore that, with the spread of effective knowledge of contraception, voluntary parenthood will become more or less universal. This will accelerate the fall in the numbers of the larger families except among those who deliberately decide to have them; but it will help to secure that children, whether in large or small families, are wanted children and are not the result of ignorance."

This is indeed an enlightened and realistic approach to the problem of family planning. It places the emphasis upon the importance of the happy and well-integrated family, rather than the large family.

2. *Scandinavian Countries.* Equally liberal is the attitude toward family planning in Sweden, Norway, and Denmark. The Swedish Population Commission, which published its report in 1935–1938, while recommending a four-child family, stressed the importance of voluntary parenthood as a means toward a democratic family and population policy. At present, Sweden has no restrictive laws on contraception. Under the very able leadership of Mrs. Elise Ottesen-Jensen, the Swedish Association of Sex Education has been conducting education in family planning for many years, and has established a number of contraceptive centers in Sweden. The clinic in Stockholm is located on one of the main streets of the city and compares favorably with some of the best clinics in the United States. Family planning is widely recognized as an essential part of the country's social welfare program. Clinics also exist in Norway and in Denmark.

3. *Holland.* Holland was among the first countries in the world to establish contraceptive services. Under the leadership of John Rutgers and Aletta Jacobs, a number of centers staffed by trained midwives and nurses were established some seventy years ago. In the 1930's, well-equipped clinics under medical direction were opened in Amsterdam, Rotterdam, The Hague, and other cities. Following the German invasion, all the clinics were closed, and a number of the physicians associated with them were arrested. Since the end of the war, however, a new association has been organized. It is functioning fairly effectively at present and has re-established family planning clinics in many cities. In spite of considerable religious opposition, these services are rapidly expanding at present.

4. *Germany and Austria.* Before the Hitler régime, Germany had a progressive and active planned parenthood movement. During the Weimar Republic, after the First World War, marriage counseling centers and birth control clinics were established in many German and Austrian cities, and much progress was being made in social and scientific aspects of planned parenthood. With the coming of the Nazi régime, however, all the centers were closed. Many of the active leaders of the movement were arrested and some of them were executed. Medical education in the field of fertility control was stopped, and the publication of medical literature on the subject ceased. The German physicians who were educated under the Hitler régime and with whom I had occasion to talk when I visited Germany in 1948 and again in 1951, had little knowledge of contraception. They had been taught in their medical schools that the use of contraceptive measures was physically dangerous and socially and racially harmful. "In this respect," an older physician, who had survived the Hitler régime, said to me last summer in Berlin, "the German doctors are now fifty years behind the stage we had reached before the war."

The legal situation with respect to the distribution of contraceptives in Germany is still confused. In 1941, Himmler promulgated a police regulation prohibiting the distribution of any intravaginal preparation designed for the prevention of conception. In many parts of Germany, presently occupied by the United States, this law is still in force. Only in East Germany, under Russian control, was the prohibitive regulation rescinded after the war.

It may be of special interest to note that, as a result of the lack of preventive measures and education in family planning, the abortion rate in Germany has increased very greatly. According to an article published in 1949 by the Goethe Institute of Medical Jurisprudence, there are more abortions in Germany than live births. For every 100 live births, there are 103 pregnancy terminations.

In some parts of Germany, however, there is at present a reawakening of social and medical interest in the problem of contraception. It is quite likely that a new planned parenthood movement will emerge in Germany as well as in Austria during the next decade in response to a growing public awareness of the social and medical needs for family planning.

5. *France, Italy, Belgium.* In Western European countries, where the Catholic religion is the predominant faith of the people, in France, Italy, Belgium, and Spain, there are no planned parenthood services. The sale of contraceptive materials and the dissemination of planned parenthood information is prohibited by law. Materials are not available in the open market, except those that can also be used for the prevention of venereal disease. While there is a growing interest and demand for adequate information on the part of the people themselves, it was my impression that there is little likelihood of any modification of the restrictive laws under the present circumstances. I gathered, however, that the rhythm method of family planning is now being increasingly practiced in many Catholic countries.

6. *The Near East.* At the present time, there is no organized family planning work in any of the Arabian countries. Neither in Egypt, Persia, Syria, Iraq, nor Lebanon are there any clinical services in contraception. A few individual physicians from these countries have visited family planning clinics in this country and in England and have obtained training in contraceptive techniques, but their services reach only a very small portion of the population in these areas.

The Moslem religion is not opposed to the prevention of conception. In an article published in the *Journal of the Egyptian Medical Association* in July, 1937, the Grand Mufti of Egypt, in a comprehensive discussion of the question, said "It is permissible for either husband or wife, by mutual consent, to take any measures to prevent semen entering the uterus, in order to prevent conception." The inadequate use of contraception in Arabian countries is therefore based primarily on social and cultural factors rather than on religious opposition.

7. *Israel.* In Israel, too, there is no organized movement for family planning. The strictly orthodox Jewish groups are opposed to the use of contraceptive measures on religious grounds, while, politically, the Israeli nation is eager to increase its numbers at present. Nevertheless, a few contraceptive services have been established in hospitals and the medical departments of the health insurance agencies, and the public health authorities are giving some consideration to the question at present. Many of the physicians in Israel today have been trained in the West and are therefore

well-acquainted with contraceptive techniques. Some contraceptive materials are now being manufactured in Israel, and they are used quite widely by couples, both in rural and urban centers.

8. *The Far East: Japan.* Under the leadership of Baroness Ishimoto, now known as Mrs. Kato, a birth-control organization was established in Japan some twenty years ago. After the onset of the Sino-Japanese War, the government frowned on the organization, and the clinics were later discontinued. At present, however, there is a re-awakening in Japan to the urgency of a planned parenthood program, and a number of centers have been reorganized.

In 1949, the Population Problem Council was established by the Cabinet of Japan was a little over 80,200,000. According to reliable estimates, it cators as members. In its final report and recommendations, the Council stressed the dangers of overpopulation in Japan. In 1948, the population of Japan was a little over 80,200,000. It is estimated that the population will rise to 90,600,000 by 1955 even with the diminishing birth rate and will reach a total of a little over 100,000,000 in 1962. "The national demand to check the population growth," the Council said, "should find its support in the idea of voluntary family planning. The important thing is that the birth adjustment should not be prescribed from outside, but voluntarily practised by each individual as a part of his design for living."

Ending the section on family planning, the report reads as follows, "We earnestly hope the above will be incorporated in the guiding principles of propaganda and also in the basic attitude of birth control to be widely practised in this country in future. The problem of emancipation of women may also find its realistic results and foothold in the enforcement of birth control along the lines as mentioned above."

In 1948, the Japanese government legalized abortions, and the number of pregnancy interruptions has gradually increased. Dr. Koya, the Director of the Institute of Public Health of Japan, in a report to the Japan Medical Congress in 1951, stated that 488,174 abortions were reported in 1950 with probably an additional 112,000 unreported, or a total number of over 600,000 abortions. "It is an amazing number," said Dr. Koya, "and such a thing has never been seen before in the demographic history of Japan." In discussing the dangers inherent in so widespread a practice, Dr. Koya stressed the importance of birth control as a major solution to the problem.

The Health Centers in Japan now have 202 Eugenic Marriage Consultation offices attached to them, and these are legally permitted to provide consultations on birth control. In spite of this, however, the birth control program is not yet widespread, according to Dr. Koya.

Dr. Koya stressed the need for the government to take on the responsibility for the improvement and distribution of contraceptive devices, as well as the need to obtain the cooperation of educators and nurses in informing the people and supplying them with the necessary materials and services.

9. *India.* India is one of the most overpopulated countries in the world, yet birth control measures are hardly known there. A number of individual Indian physicians have interested themselves in the subject, and clinics have been established here and there, but their number is small and they have

been able to reach only a tiny portion of the Indian population. Recently, however, an Indian Family Planning Association was organized.

In 1946, a Health Survey and Development Committee, appointed by the Indian government, recommended, among other things, that free contraceptives be supplied by the state whenever further pregnancy would be detrimental to the health of the mother. There are no legal or religious prohibitions against the use of contraceptives among the Hindus, although the teachings of Gandhi, who was opposed to contraception and advocated continence as the only method of family limitation, still have a very wide influence in India.

The Indian government, however, has recognized the vital importance of family planning for that country. In a discussion of the problem in April 1951, Nehru, the Prime Minister, said, "I am entirely in favor of limiting the growth of the population by institution of various methods, including birth control."

This attitude is now being implemented by a practical plan. The Minister of Health of India has very recently requested the World Health Organization to send a medical consultant and two social workers to India to establish a pilot study on the use of the rhythm method of contraception in India. This is the first official action in this field by any government. Out of it, perhaps, will grow a wider recognition of the importance of family planning as a health and a social measure for India.

10. *China.* China, too, is a very much overpopulated country. The fertility is high and the social and cultural forces responsible for the high rate of reproduction still prevail. In their report of a survey trip made in 1948, Balfour and his co-workers state that there is still little appreciation of the need for reducing the birth rate among the political leaders and older scholars. Efforts to permit birth control by means of contraception have been made by certain groups, and there is indication that many women do want to limit their childbearing, yet the activities of the few birth control clinics have been rather meager.

More recently, the mass education movement in China has been interested in introducing birth control measures, but the progress of their program is not known at present.

11. *Russia and Its Satellites.* What is happening in the field of family planning in the Soviet Union and in the countries under its control? When I visited the Soviet Union in 1935, there were no restrictions against the dissemination of contraceptive information, and materials were freely available. Russia had legalized abortions, and the health authorities were urging the use of contraceptive measures as a means of avoiding abortions. Notices were posted in gynecological hospitals urging women to seek contraceptive advice rather than resort to abortions. It is true that the materials available at the time were meager and of poor quality, but at least they were freely available to those who wished to use them.

In 1936, the abortion law was rescinded, and the distribution of contraceptive material considerably curtailed, as far as I can learn. No prohibitive laws against the dissemination of contraception have been enacted, but the social and cultural pressure is to-day toward a larger population and against the use of methods for controlling fertility.

What applies to Russia probably applies also to Poland, Rumania, Bulgaria, and Czechoslovakia. Just before the political change in 1948, I visited Prague and I found no birth control clinic and no birth control materials. I doubt very much whether the situation has altered since.

12. *The United States.* The rapid acceptance and diffusion of family planning practices in the United States has been one of the significant social phenomena of our history It was less than forty years ago that Margaret Sanger began her epochal campaign for voluntary parenthood and coined the trenchant and expressive term "birth control." Today the idea and the practice of conception control have become an integral part of our social mores. Religious, professional, and legal barriers have broken down, and family planning is now a widely accepted social practice in this country.

Medical progress has also been striking. Thirty years ago, there was not a single birth control center in the United States, hardly a medical paper was published on the subject, there was no medical instruction in any of the colleges, and no research in the field of conception control was being carried on. Today, family planning centers have been established throughout the country. In a number of states, public health departments have actually integrated the provision of contraceptive information into the public health services. Contraception has become a recognized part of medical training and research in the field of human fertility and its control is now being carried on in a number of our leading universities and laboratories.

Interest in family planning is today developing rapidly all over the world. From reports that have come to the International committee on Planned Parenthood, there are some forty areas at present in which family planning services are either available or where organizations for education in the field have been established. Among these areas are Australia, Austria, Barbados, Bermuda, Canada, Ceylon, Denmark, England, Egypt, Finland, Germany, Holland, Hong Kong, India, Israel, Italy, Jamaica, Japan, Malaya, New Zealand, Norway, Pakistan, Puerto Rico, Singapore, South Africa, South Pacific Islands, Sweden, Switzerland, and the United States.

The worldwide need today in the area of family planning is twofold: mass education, and mass production of a simple, practical, reliable, and inexpensive contraceptive method.

Modern medicine has made tremendous advances in decreasing the death rate the world over; yet the birth rates have hardly been affected in many areas. To bring about some balance between world populations and world resources, some form of population planning is essential. We cannot have continued death control without any accompanying birth control. This is the basis for an international program of family planning on health and social grounds.

POPULATION CONTROL BY PERMANENT CONTRACEPTION

By Clarence J. Gamble
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Among the methods of controlling undue population expansion, permanent contraception by surgical means is of importance. As it involves no change which the patient can detect, except that children are not produced, the personal cost, when the protection is desired, is not large. Salpingectomy, by the usual surgical methods, requires a well-equipped operating room and hospitalization for the healing of the wound, so that the initial cost is high, compared with temporary forms of birth control. There are no recurring costs for supplies, however, and the results cannot be vitiated by an omission or by the patient's carelessness or faulty technique. It seems probable that if a program of population control is arranged on the usual basis of a public health procedure, the cost of each salpingectomy will not greatly exceed that of birth control supplies and the distribution and supervision involved during the remaining fertile years.

Because the vas passes so close to the surface of the body the operative technique for sterilization of the male is simpler and hospitalization in the usual sense is not required. In most societies, however, the male patient will require more explanation than the female to convince him that a sterilization does not require undue sacrifice.

If the intra-uterine cautery technique of Dickinson[1] can be made more widely available, it is possible that the total costs of effective protection from parenthood can be reduced below that of any of the other presently accepted methods of contraception.

Dickinson placed the tip of a uterine sound, bearing an electrically heatable platinum wire, in the cornu of the uterus, guiding it by touch. Turning on the current for a few seconds heats the surrounding tissue so that a scar forms, obstructing the tube.

The method has since been elaborated by Hyams,[2] who injects iodized oil into the uterine cavity and observes his instrument by fluoroscope. To supply the heat, he uses radio-frequency electrical current. In a certain proportion of cases in which the scarring is incomplete, both methods require subsequent testing for completeness of closure and re-cauterization. The methods make the occupancy of a hospital bed unneccessary, and, in the Dickinson method, or in that of Hyams, if touch rather than the fluoroscope is relied on, the cost of the apparatus is not great. With adequate testing and public education, these methods may provide a valuable antidote to balance the overpopulation engendered by public health methods of mortality reduction.

Sterilization has not yet been widely used as a means of population control. The experience in Puerto Rico indicates that it will be acceptable when adequately understood. A well-known obstetrician in one of the Island's charitable clinics makes the statement, "Every woman coming to the clinic asks for sterilization." The popularity of sterilization is also indicated by the rate of these cases in the governmental hospitals. It is said that this rate rises before each election, because the politicians give political favors by recommending admissions to hospital beds for sterilizations.

More definite evidence of wide acceptance of permanent birth control comes from Japan.[3] Under that country's Eugenic Protection Law, 5,749 sterilizations were reported in 1949, of which 5,604, or 97.5 per cent, were performed at the discretion of the physician, with the consent of the individual and the spouse. In 1950, the number rose to 11,403. 7,477 sterilizations were reported[4] in the first six months of 1951, a further increase in rate.

The chief limitation on further sterilization in Japan is the present lack of hospital beds. Intra-uterine cautery sterilization is being tested and may expand the numbers in future years. It is believed that the growing appreciation of overpopulation in the family and in the nation has much to do with the growth in the number of sterilizations and that, in many cases, health reasons are secondary, rather than primary. The increase shows that permanent birth control is an acceptable method, especially when the need is reinforced by population pressure.

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MEDICAL AND MEDICO-SOCIAL INDICATIONS FOR CONTRACEPTION

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For whom should a physician prescribe contraceptives? If the question involved the prescription of insulin, or even penicillin, there would be relative agreement. Purely medical considerations are involved in such cases. The field of conception control, however, is compounded from a small amount of medicine diluted by a large amount of religion and social mores. A particular doctor's answer to the question, "Who should receive contraceptive advice?" is not only influenced by his religion and social origin, but also by age, medical-school training, the hospitals in which he practices, and his medical specialty. In the main, younger and more recent graduates are more liberal in their attitudes toward birth control.

In 1947, the writer[1] sent a questionnaire to fifteen thousand physicians scattered throughout the United States, one-third of whom were specialists in obstetrics and gynecology, and the rest general practitioners. The purpose was to establish a cross-section of medical opinion in regard to conception control. Some 3400 physicians replied. Only seventy-four of these stated that they did not approve of contraception for any medical condition, leaving a striking majority (97.8 per cent), who believed that at least some health problems necessitated contraception.

In addition to the purely medical aspects of the survey, these 3400 physicians expressed approval or disapproval of conception control for other reasons. Seventy nine per cent approved of contraception for economic reasons, and 72 per cent approved it as an aid in marital adjustment. The final question was "Do you approve of contraceptive advice being given to any married woman who requests it?" In other words, does the physician believe that it is every married woman's medical birthright to receive the best available scientific birth control knowledge? Sixty eight per cent answered this very broad question in the affirmative. If this questionnaire mirrors the opinions of a representative cross-section of American physicians, and we believe it does, one may say that seven out of ten doctors feel that any married woman desiring birth control information is entitled to it.

To return to the purely medical aspects of the survey of physicians, we sought to determine the more common health problems for which doctors approve conception control. The question was "Do you approve of conception control for the following conditions (assuming conditions are more than minimal)?" Twelve common health problems were placed in alphabetical order and blanks were placed after each ailment to record a "yes" or "no" answer, indicating approval or disapproval of the ailment as an indication for birth control. No single indication polled 90 per cent approval, although almost 98 per cent of the answering doctors approved of conception control for at least one medical reason.

Pregnancy Spacing. Most physicians probably have had the question "What is the optimum interval between babies?" asked of them repeatedly.

It is a difficult question to answer, partly because the correct answer is based on many medical, social and economic factors. Let us focus on medical considerations, leaving the social and economic factors to the sociologist and the economist.

The survey referred to earlier sought to determine the proportion of physicians who consider child-spacing sufficiently important to justify the prescription of contraception. More than 86 per cent of the some 3,000 physicians replied affirmatively to the question, "Do you approve of conception control for child-spacing?" Only two medical indications competed with it in popularity. Cardiac disease polled almost 89 per cent and pulmonary disease tied child-spacing for second place in approval (TABLE 1).

TABLE 1

Indication	*Per Cent*	
	Yes	*No*
1. Cardiac	88.8	11.2
2. Pulmonary disease	86.5	13.5
3. Renal disease	84.0	16.0
4. Nervous and mental disease	83.5	16.5
5. Great multiparity	79.6	20.4
6. Hypertension	79.2	20.8
7. Diabetes	76.0	24.0
8. Ex-opthalmic goitre	73.8	26.2
9. Prevention of inherited disease or malformations	72.4	27.6
10. Recent pelvic operation	71.5	28.5
11. General debility and anemia	69.5	30.5
12. Venereal disease	66.0	34.0

Medical Optimum. The medical optimum interval between the termination of one viable pregnancy and the beginning of the next has even the experts puzzled. Any scientific answer should be based on an analysis of the relation of the birth interval to maternal mortality and morbidity, as well as its effect on stillbirths, neonatal deaths and infant mortality.

There have been four significant studies in this field: Hughes (1923),[2] Woodbury (1925),[3] Eastman (1944)[4] and Yerushalmy (1945).[5] The two earlier studies, based on small samples, analyzed only the infant mortality rate during the first year of life, in relation to the birth interval. The conclusion of the two studies were identical. The infant mortality rate was highest when the birth interval was less than two years, and relatively the same for all longer intervals (Woodbury,[3] 146.7 per 1,000 for periods of less than two years duration, and 98.6 to 84.9 per 1,000 for longer intervals).

The impact of the Hughes and Woodbury studies on the pattern of childbearing in this country was tremendous. It was argued that child spacing was virtually essential for the survival of the nation and pregnancy spacing became one of the chief cornerstones of the Planned Parenthood Movement.

Both Eastman and Yerushalmy conducted studies essentially different from those of Hughes and Woodbury. It will be recalled that the latter two had analyzed the effect of the birth interval on only one category, namely, infant mortality during the first year of life. Eastman, on the other hand, studied its influence on abortion, premature delivery, stillbirths, neonatal deaths, maternal toxemia, *post partum* hemorrhage, puerperal infection, ability to breast feed and maternal mortality; in summary, its effect on almost every factor except infant mortality.

Eastman divides his study into two parts. The first included 5,158 patients delivered at the Johns Hopkins Hospital, cases in which the interval between the previous viable delivery and the termination of the present pregnancy was accurately known and recorded. This group was termed the direct series. The second part reviewed 33,087 obstetric cases in which the interval between births was not recorded but age and parity were. Eastman said, "By correlating these two factors (particularly great parity in younger age groups) it was possible to draw conclusions indirectly about the effect of rapid childbearing (and hence short average intervals) on maternal and fetal prognosis." This group was termed the indirect series.

Eastman drew the following conclusions from these two studies: (1) "Infants born from twelve to twenty-four months after a previous viable delivery (that is during the second year) have at least as low a stillbirth and neonatal mortality as do infants after longer intervals." (2) "The longer the interval between births, the more likely the mother is to suffer from some form of hypertensive toxemia. . . In patients who have had a previous hypertensive toxemia the likelihood of repetition becomes progressively greater as the interval becomes longer." None of the other conditions studied by Eastman, *i.e.*, premature labor, anemia, *post partum* hemorrhage, *etc.*, showed a positive correlation with the birth interval.

Yerushalmy's study was based on a huge sample of total viable births in the United States (7,151,631), during the five-year period 1937–1941. By the same indirect method that Eastman employed, Yerushalmy analyzed the effect of the birth interval on only one item, the stillbirth rate. Yerushalmy concluded "that relatively short intervals and relatively long intervals are associated with higher stillbirth rates while the moderate intervals lead to the lowest rates." He does not define his various intervals in months or years. Contrary to Eastman, Yerushalmy feels that the birth interval affects the stillbirth rate far more shan the mother's age.

It is difficult to reconcile the four studies; in fact, even a comparison is difficult. To summarize each in a sentence or two: On the basis of very small samples, now more than twenty-five years old, Hughes and Woodbury found that babies born very close together (less than two years apart) had a materially reduced chance of surviving the first year of life. It would be of interest to determine whether a statistically significant modern sample would corroborate this finding. Eastman found that the birth interval was relatively unimportant to the reproductive welfare of the mother or the survival of her baby. He felt that the mother's age was a more important factor in successful childbearing than that of pregnancy spacing. Eastman's sample was small and heavily weighted with the abnormal obstetrical material which ordinarily gravitates to a large urban University clinic. Yerushalmy, on the basis of a thoroughly adequate sample, concludes that, when only the occurrence of stillbirths is under consideration, a "moderate" birth interval is superior to either a "short" or "long" one. From this summary, it is obvious that further modern studies on valid samples are essential before one can give a scientifically correct medical answer to the very important question, "What is the optimum birth interval?"

When there are no scientific data to answer a medical question, the clinical intuition of a group of doctors may fill the void. After all, clinical intuition is really the summation and analysis of multiple clinical observations.

The replies of three thousand physicians[1] to the questionnaire query, "How long should pregnancy be deferred between babies?" supplies part of the answer for the optimum interval. The average interval agreed upon was 14.1 months from the termination of one viable birth to the beginning of the next pregnancy, or a minimum safe interval of 23 months between children. Half of the respondents considered 10 to 18 months a safe interval between pregnancies or, differently expressed, 19 to 27 months between babies. (No statement was sought in regard to the most desirable interval or a safe maximum interval.)

I know of no scientific data to advise the patient on the optimum interval between spontaneous abortion and another pregnancy. The respondents to the physicians' questionnaire,[1] on the basis of their clinical judgments, wrote very different answers to the question which sought this information, but the average of the intervals suggested in the replies was 6.6 months.

The above data, then, constitute a summary of the general medical attitude toward conception control, primarily the attitude of the physician toward strict medical indications. With the above information as an introduction. I would like to express my own opinion in regard to medical and medical-social indications for conception control.

The goal of every pregnancy is a healthy normal baby, born to a mother whose life is neither temporarily jeopardized nor permanently injured by its advent. If this formula is broadly applied, it will determine what pathological conditions make pregnancy ill-advised. Whenever pregnancy is contra-indicated, either contraception or sterilization is indicated.

If the pathological condition seems to be temporary, irrespective of the patient's age, contraception is indicated and sterilization ruled out. On the other hand, if the condition interdicting pregnancy is permanent, with no likelihood of improvement, sterilization is the wiser choice This is particularly true if the woman is young and has many more fertile years. If the woman is a carrier of hemophilia, or has given birth to a series of abnormal children, sterilization is wise and proper. On the other hand, if she bears erythroblastotic children, a disease recently unraveled and constantly being worked upon, contraception is preferred to sterilization. I say this because in the next twelve months someone may discover a method of preventing erythroblastosis, which is not a germ plasm defect, but simply an immune reaction on the part of the body to a foreign substance, the Rh factor, which the host herself does not possess.

Every experienced obstetrician develops his own ideas about pregnancy spacing and, with some misgivings, I will state mine: It is no medical tragedy if babies follow each other in rapid succession. If a pregnancy terminates in fetal death, or if the woman is in her mid-thirties when she starts her family, contraception is recommended only until the end of the third month *post partum*. Similar advice is given if fibroids threaten hysterectomy in the next few years. If everything is normal, however, and if the woman is young, a minimum waiting period of fifteen months and a maximum of twenty-seven months between pregnancies is recommended. Such children would be born two to three years apart.

When a patient aborts spontaneously, the type of abortion determines my advice. If it is an early abortion, twelve weeks or less, and defective germ plasm is the cause, the basal metabolic rate is obtained one week post-abortion. If thyroid therapy is indicated, contraception is advised for the first two months while thyroid medication is being taken. Then, after two months of continuous thyroid therapy, contraception is abandoned but the thyroid therapy continued. If the basal metabolic rate proves thyroid medication unnecessary, re-impregnation is allowed as soon as all staining ceases. If the abortion is later than twelve weeks, when defective germ plasm is rarely the cause, contraception for six months before starting another conception seems to yield the best results.

These are my opinions about the medical indications for conception control as of October 20, 1951. New data may very well modify them six months hence.

My attitude toward medico-social problems involving conception control follows. Young people should be put in the position to marry while they are still young without the harassment of impending pregnancy—pregnancy before they are economically or emotionally prepared for it. Premarital contraceptive advice by a physician is extremely wise for the intellectually mature woman. Sexual adjustment at the onset of marriage is much better mental hygiene than maladjustment followed by remedial measures.

Children are tragic cement to bind together a marriage separating at the seams. If there is any doubt about the stability of a marriage, postponement of children is very important until the disharmonies are securely adjusted. It does not require a physician to point out the economic necessities for conception control. I dare say that most underprivileged couples who produce an annual model do not do so from choice. Furthermore, jurists, doctors, and social workers are similarly aware of the tie-up between poverty, huge families, and juvenile delinquency.

The problem of contraceptive advice for the unmarried is a very complex one. I am unwilling to accept the ostrich-like moralistic viewpoint that such a problem does not exist; it did not require the Kinsey report to prove that premarital intercourse is common practice. I readily admit that I cannot give the proper answer to the question of whether the unmarried youth of our country should be scientifically advised and instructed in birth control. Furthermore, I do not believe it can be done. The proper answer must depend on more Kinsey-like studies. Knowledge must replace taboo and prejudice.

Finally, there is the world picture, the inter-relation of population density and population growth with the standard of living and the geographical area of a political unit—problems which have already been discussed by other authors in this monograph.

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Discussion of Paper by Doctor Guttmacher

Doctor Sophia J. Kleegman, *Associate Clinical Professor of Obstetrics and Gynecology, New York University College of Medicine:* For whom should a physician prescribe contraceptives? May I call to your attention that the Medical Advisory Committee of the Planned Parenthood Federation of America, a group of distinguished physicians representing varied branches of medicine, spent a great deal of time, thought and discussion on this very question. After careful joint thinking and pooling of experience, they drew up a list of Medical Indications for Contraception which may be obtained from them.

The first session of this present conference was devoted to discussions of problems of world population. Statistics are very impersonal. Problems of hundreds and thousands are translated to the clinician as they affect the individual man, his wife, and his family. The physician must consider primarily each family unto its own needs, and the needs of the community secondarily.

Dr. Guttmacher speaks of medicine diluted by religion and social mores. Certainly, in this country, when we discuss the persons for whom a physician should prescribe contraceptives, a part of medical practice, medicine is not diluted by religion. It is ruled by a minority religious group and runs contrary to the actual practices of the majority of the people.

Our choice, therefore, lies between haphazard, unsafe, unreliable methods of contraception or the prescription of safe, medically approved measures for planning the size of the family.

This is the age of preventive medicine. This means not only the prevention and cure of disease but also the promotion of total health—physical, mental, and emotional.

The best preventive medicine for criminal abortion is medical advice on how to have children when children are wanted. Fear of pregnancy is a destructive force in a home. A physician soon learns that a safe method of contraception promotes wholesome sex life and furthers emotional health in the family unit.

In Massachusetts it is legal for a physician to perform a therapeutic abortion but it is illegal for the physician to then prescribe a safe method of contraception for such a patient.

This is a scientific monograph and yet I would like to present a problem of morality or ethics in this phase of medical practice.

Basing his statement on the answers he received to his questionnaire, Dr. Guttmacher says that seven out of ten physicians believe in their hearts that prescribing contraceptives is a legitimate part of medical practice.

It is impossible, however, to establish a contraceptive clinic in most city and county hospitals which take care of the indigent. The patient in the higher economic group who has just had a baby has every opportunity to obtain contraceptive advice if and when she wants it. The poor are denied this same opportunity and freedom of choice in determining the arrival and number of their children.

Such a disparity of medical service is unethical. Some of this indigent group are reached by the Planned Parenthood Clinics. Reaching these patients is one of the goals of democratic living which the medical and allied professions must achieve. People in all economic levels must be offered equal opportunity for freedom of choice in planning for their children.

I know of one obstetrical service for the indigent where a woman having six living children can have postpartum ligation of her tubes if she and her husband request this procedure and if there is some additional indication. On the other hand, the physicians of this very same service accede to this request from their private practice group after the fourth or even third delivery if the couple are very desirous of this procedure.

Should every woman be given contraceptive advice on request? My answer is "No." There are contra-indications to, as well as indications for, contraception. In many cases, we would be offering our women poor medical service if we gave contraception on request and without discrimination. After a careful interview and counseling, if the woman is sure that she never wants children, then contraception is indicated. A woman who rejects maternity "forever" is emotionally ill, unless there is a serious genetic or medical reason for not having children. For the couple who say, "We want children very much, but not now," then it is the physician's obligation to ascertain the reasons for postponement of parenthood, and weigh the urgency of the reasons against the chances of jeopardizing future children by postponement. Does the couple have physiological leeway for postponement? How old are they, and are there any evidences of poor potential fertility in either mate?

We know that medically approved measures of contraception do not reduce fertility, but time does, especially for the woman. If she does not marry until near or past thirty, less time is left for emotional adjustment, waiting for a college degree, or economic security. The desired security may come when the opportunity for fertility has slipped by. I have always urged, even in Planned Parenthood Clinics serving the lower economic group, that indications for continued use of contraception should be re-evaluated every two years.

Most couples in the more favorable economic and educational levels do not meet their parental obligations adequately, and should be encouraged to have more children. Dr. Guttmacher recommends that children should be postponed until discordancies are securely adjusted. Have we placed undue emphasis on security—on this perfect adjustment? I'm sure that Dr. Guttmacher and I would probably agree in the individual case. There should be a period allowed after marriage for emotional adjustment—depending upon the age of the couple—but we cannot wait too long for this perfect and secure adjustment. We must face the prospect that each year and, particularly, each child brings new problems which are to be faced and worked through while the children are expected and while they are growing.

In summary, for whom should a physician prescribe contraception? A physician should prescribe contraception for the same indications, and with equal freedom of choice, for rich and poor, for private patient and indigent ward patient and for the same indications for which the physician prescribes contraception for his own wife and his own daughter. I will close with the incomparable Robert L. Dickinson's dictum, "Every couple should have as many children as can be safely carried, safely born, and adequately reared."

Discussion of Papers by Doctors Ford, Stone, Gamble, and Cook

DOCTOR HALBERT DUNN, *Chief, National Office of Vital Statistics, National Institutes of Health, Washington, D. C.:* It is suggested that the discussants assume that there is no difference of opinion with respect to the fact that a world population problem exists, as set forth in the previous papers, and that something must be done about it. It is suggested that the entire discussion orient around the problem of obtaining an action program in this field, realistically recognizing the prejudices, nationalism, and other difficulties involved.

In many ways, the people are ahead of their leaders in the frank recognition of the necessity for some sort of fertility control. In addition to the fertility control practices of more primitive tribes of people discussed by Dr. Ford, the different approaches now being made by various nations as described by Dr. Stone, and the method of population control through permanent contraception (sterilization) as set forth by Dr. Gamble, there is at least one big gap which should be explored, namely, the possibilities of obtaining population control through some temporary, but positive, fertility control mechanism.

It is conceivable, for example, that chemical agents might be found which could be added to common table salt and which would cause temporary infertility in much the same manner as the control of exophthalmic goiter through the addition of iodine to salt. Or the answer might come from the development of some sort of a vaccination or inoculation against pregnancy which would be effective for a specified period of time, such as one or two years. If methods of fertility control could be found which are positive but temporary in nature and which would not have to be exercised during the act of sexual intercourse, a program of fertility control could be directed with much greater certainty in areas of population pressure. A positive type of temporary fertility control of this character would also more or less automatically take care of the differential genetic deterioration brought out by Mr. Cook in his discussion of problems of population control.

BIOCHEMICAL STUDIES OF THE FEMALE GENITAL TRACT

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Among the mammals, the human being is relatively non-prolific. Social, economic, and medical considerations, however, are obviously making the wise control of human population an immediate necessity. A solution to the problem of simple, effective means for such control would be perhaps the most important contribution of the biological sciences at this time. It is very appropriate, then, that we consider the biochemical studies which have been made of the male and female reproductive systems, since an understanding of these systems, as they function on the cellular level, may be expected to provide further valuable bases for techniques of preventing pregnancy as well as treating sterility.

The cyclic occurrence of periods of reproductive ability in the female is a fairly uniform feature among the mammals. From menarche to menopause in the normal woman, as in most animals studied, the entire reproductive tract shows striking changes at quite regular intervals, seemingly designed to facilitate the union of the spermatozoa and the newly-matured ovum, and to aid the implantation and growth of that ovum in the event of its fertilization. If pregnancy is not realized, the background for fertilization regresses, and then is again prepared. These cyclic changes, under the control of the pituitary and ovarian hormones, appear to depend not only on the absolute amounts of these hormones but also on their ratio and sequence.

Certain natural limitations on experimental work with human beings require that voids in our understanding of human biochemistry must be filled temporarily by data from the more abundant knowledge derived from lower animals, with the recognition that conclusions from experiments on one species do not necessarily apply to others. In comparison with the thorough histological examination of the female reproductive tract in all phases of the menstrual cycle, the biochemical examination, especially in the human, is even then in its highly incomplete infant stage, and is often confusing with its profusion of seemingly-unrelated bits of information. At the moment, we will be concerned principally with some of the studies made on tissues which provide the immediate environment of the spermatozoa, the ovum following rupture of the follicle, and the fertilized egg, *i.e.*, concerned principally with the epithelial lining of the reproductive tract. Only briefer mention will be made of certain aspects of the biochemistry of other tissues of the reproductive system, *e.g.*, the musculature.

It must be emphasized at the outset that, while all normal women show essentially the same sequence of events in these cyclic reproductive changes, the time intervals in the sequence vary considerably in different women, and even in the same woman, during different cycles. It is this fact which largely invalidates the rhythm method of contraception. The interval between ovulation and the beginning of the next menstrual period appears to be one rather consistent period of time in a particular woman, but may be eight to ten days in one, or even seventeen to nineteen in another, with the average at about fourteen to sixteen days. Therefore, no attempt will be made here to place the biochemical events described at specific intervals by days in a menstrual cycle of any specific length. In this connection, it would be of interest to study differences in various population groups in time of occurrence of ovulation, similar to the studies of differences in age of onset of menstruation and of fertility.[1]

In contrast to the intra-uterine deposition of spermatozoa in some mammals, the intravaginal deposition in the human female would seem to provide the sperm with an unfavorable environment, since the normal vagina is acid in all phases of the cycle. Acidity, detrimental to the metabolism of spermatozoa, does not allow their motility to continue for any prolonged period of time, once the buffering capacity of the seminal plasma has been exhausted. The acidity of the vagina appears to be due principally to lactic acid from the breakdown of the abundant glycogen present in the epithelium in all phases of the cycle. In fact, the presence of glycogen under normal conditions in women during the reproductive years is so consistent that its loss from the epithelium in certain abnormal states, including carcinoma, has served as an early means of locating the areas, particularly those on the exterior of the cervix, for further examination by biopsy.[2] Although cyclic changes in the vaginal epithelium are far less pronounced in the human than in rodents, a definite rhythm can be noted, which has been correlated with the cyclic influence of the ovarian hormones, principally estrogen. The mobilization of glycogen is increased with the onset of increased estrogen production of the ovulatory phase. The cyclic changes have been followed by quantitative methods in the monkey[3] and estimated histologically in the human. Concurrently, the acidity shows some increase, *e.g.*, the pH fell from an average of about 4.9 to about 4.2 in one careful study of more than 600 determinations. (See bibliographical reference 4 for a detailed discussion of all of these aspects of vaginal biochemistry.)

The acidity of the vagina, while it offers the sperm a rather unfavorable environment, may simultaneously provide the female with a protective mechanism against bacteria less innocuous than those present. Fortunately, too, a number of spermatozoa quickly escape, at least in the ovulatory phase of the cycle, into the more propitious environment of the cervix before their motility has been adversely affected by the acidity.

The cervix, or, more specifically, its mucous secretion, undergoes striking cyclic changes which make it particularly receptive to spermatozoa in the season of ovulation. Even on gross observation of the cervix, it is obvious that, shortly after cessation of the menstrual flow, the secretion is small in amount, very viscous and cellular, while the external os is later visibly enlarged and a clear watery secretion, very similar to egg white, issues from it. After four or five days, the flow of mucus again diminishes to the preceding state, *i.e.*, little visible secretion. The periodicity of changes in type of mucous secretion was recognized as early as 1855,[5] but only more recently has it been shown to be under the influence of estrogens[6–8] and definitely correlated with the ovulatory phase* of the menstrual cycle.[9]

Human spermatozoa require certain carbohydrates for energy in their motility[18–20] and undoubtedly can carry with them little supply from the seminal plasma on migration through the cervical mucus. Perhaps of greatest significance, then, is the presence in the mucus (in all phases of the cycle) of the sperm-utilizable carbohydrates glucose, maltose, and glycogen and an enzyme, diastase, capable of breaking down glycogen to the more readily used glucose and maltose.[14] That the spermatozoa can use these sugars as they occur in the mucus is suggested by the discovery that incubation of washed sperm with cervical mucus causes a 100 per cent greater decrease in the sugar content of the mucus than incubation of mucus alone.[21]

Seventeen amino acids have been identified in the cervical mucus.[22] The lipids, about half of which are cholesterol and phospholipid, have also been determined throughout the intermenstrual cycle.[23] While neither amino acids nor lipids appear to be utilizable by human sperm for motility,[18] they are felt to contribute favorably to the total environment. *In vitro* animal experiments indicate that lipids, apart from any nutritive value they may possess, exert some protective action on spermatozoa and prolong viability.[24]

The sodium chloride concentration of sperm-containing media, through its effect on osmotic pressure of the media, has also been found to affect sperm motility.[25] Although cervical mucus has some cyclic variation in osmotic pressure, due principally to its sodium chloride content, the osmotic pressure throughout the cycle is within the range which favors most prolonged sperm motility. Of established importance is the fact that the cervical secretion is alkaline in the majority of cases in all phases of the cycle.[26]

Another facet of the chemical composition of cervical mucus had been suggested by evidence that the mucus may check the growth of some strains of *Streptococcus hemolyticus* and *Staphylococcus aureus*.[11] The recent demonstration of a definite lysozyme-like inhibitory action of the mucus against *Micrococcus lysodiekticus* is additional positive evidence of a natural antibiotic activity of the secretion. While this organism is saprophytic, laboratory tests show the mucus to be more effective in arresting its growth than is penicillin in the usual test doses.[27]

Biochemical studies of the cervical environment of spermatozoa are complicated first by the small amounts of secretion which can be obtained at one time for study—often only 10 or 15 mg. during the pre- and post-ovulatory phases and 400 to 700 mg. at the very most, even during the ovulatory phase. Also, the fact that such a high percentage of each sample aspirated is water, means that all other constituents are present in very small absolute amounts, and require very sensitive methods for their determination. Nevertheless, the cervical environment is well suited for studies of the day-to-day changes throughout the menstrual cycle in the normal healthy individual, since mucus can be aspirated daily, cycle after cycle, from the same woman without altering the normal functioning of the cervical tissue. On the other hand, the uterus, to which the sperm progress from the cervix on their way to meet the ovum, presents a new set of difficulties, especially in the human, in regard to biochemical studies. Endometrial biopsies cannot be taken daily, cycle after cycle, and so one must be content to examine only a few, often single, specimens from any one woman. Conclusions about cyclic variations must therefore be drawn from comparison of results on different women in the various phases of the menstrual cycle, recognizing the wide degree of individual variation within the normal range. Many of the studies reported necessarily have been carried out on material from operative specimens or on biopsies from sterility cases. Nevertheless, certain facts and patterns become evident from the accumulation of data.

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* The term "ovulatory phase" will be employed since the coincident changes clinically observed to coincide with the approximate time of ovulation—the peak of the outpouring of cervical mucus, the shift in basal temperature, the changes in vaginal cytology and in basal metabolic rate, the appearance of pregnanediol in the urine—are the body's response to the particular hormonal influences existing at the time of ovulation, but are not the direct and immediate result of ovulation itself. They indicate the season, not the hour, nor even, necessarily, the day of ovulation.

Sperm reaching the uterus around the time of ovulation continue to find a favorable alkaline environment. As the epithelial lining of the uterus has been growing and proliferating under the influence of estrogen and preparing to receive the ovum, the deposition of glycogen has also been progressing. The significance of the high concentration of alkaline phosphatase in the endometrium at this time[28, 29] is as yet undetermined. The evidence on the physiological role of this enzyme is still predominantly for degradation, *i.e.*, hydrolyzing various organic phosphate esters, not for synthesis.[30] This should be remembered in evaluating the various hypotheses which have been presented on its functions in the increased uterine protein production and cell division, the lipid metabolism and the glycogen deposition.[29, 31, 32]

A high concentration of the enzyme β-glucuronidase has been produced in the endometrium by the injection of estrogen into ovariectomized mice[33] and has been found in women in the uterine epithelium during the first two-thirds of the cycle.[34] Involvement of the enzyme in transport or metabolism of the ovarian hormones and possibly also in the incorporation of glucuronic acid in this period of epithelial proliferation in certain intracellular substances, such as the mucins, has been suggested. Some who doubt its unproven role in synthesis *in vivo*, assign the enzyme a function in cell division independent of synthetic activity. (See bibliographical reference 35 for more detailed discussion.) The value to the uterus of these cyclic variations in β-glucuronidase, like those of alkaline phosphatase, must, therefore, await elucidation.

The newly-matured ovum, at some moment in the ovulatory phase, is expelled from the ovary and enters the fallopian tube, which provides for its passage to the uterus. In the human, both glycogen and lipids have been demonstrated histochemically in the epithelial lining of the tubes,[36, 37] but have not been quantitatively determined, and other biochemical determinations on this portion of the reproductive tract are meager. Since the site of fertilization is the outer part of the fallopian tubes in most mammals, the chemical constituents of the tubal epithelium may be of environmental significance for the spermatozoa as well as for the ovum. In view of the evidence for the importance of tubal contractions in transport of the ovum to the uterus, an examination of the energy metabolism of the musculature of the tubes also would be of considerable interest.

A detailed consideration of ovarian metabolism is beyond the scope of this discussion. Some of the unique biochemical aspects of the ovary (which might be anticipated from its very specialized functions both before ovulation and after the corpus luteum has been formed) should be indicated, however. The lipid composition of the follicle and of the corpus luteum has been noted to vary with functional activity in a number of species and has led to the hypothesis that the lipid metabolism is intimately concerned with synthesis of the ovarian hormones.[38–41] Vitamin C also has been implicated in some species in the synthesis of these hormones, both because of the marked variations in its concentration in the follicle and lutein tissue and because a dietary deficiency of this vitamin causes degeneration of the corpus luteum.[42–43] Enzymes which may be involved in the energy requirements of a secretory gland such as the corpus luteum have been investigated rather extensively in rat lutein tissue.[44–46] A relationship between follicular growth and glycoprotein content of the granulosa cells also has been suggested[47] from work on the rat.

Following ovulation, the uterine epithelium continues to prepare a suitable environment for implantation and nourishment of a fertilized ovum. Glycogen is deposited in still greater amounts,[48–50] probably due to the enzyme phosphorylase which is present in particularly high concentrations during this phase of the cycle.[51] Another enzyme, a diastase similar to the one in the cervical mucus, also shows an increased concentration, and is thought to be concerned with breakdown of the glycogen to simpler sugars which are more readily utilizable by the ovum.[52]

In contrast to the eggs of oviparous and ovoviviparous forms, which contain an adequate food supply for the entire development period, ova of the placental mammals contain very little. While glycogen has been demonstrated in the rat ovum[53] and a yolk nutrient in the ovum of the hamster,[54] the fertilized ova of these and the other higher mammals appear to become dependent soon on the maternal organism for their nutrition. In fact, glycogen lack in the human endometrium in the post-ovulatory phase of the cycle has been correlated with spontaneous abortion and sterility.

The lipid content of the endometrium also shows an increase and a shift in position of the lipids within the cells during this phase following ovulation.[55] Although the evidence for the human has been derived largely from the staining of tissue sections, quantitative determinations of cyclic variations in neutral fat, phospholipid, and free and esterified cholesterol have been made in the monkey[56] and the sow[57] and have shown certain species differences. In the same species, chemical methods do suggest the presence of more lipid in proliferative endometrium than is demonstrated histologically. This may be partially explained by the fact that lipoproteins do not respond to usual lipid staining, but are alcohol-ether extractable and so contribute to the lipids chemically determined. The relation of the individual lipid constituents to physiological activity in the uterus is still entirely speculative.

The changing pattern of enzyme systems with changing properties of the tissue has been reflected in the endometrium in manometric measurements of anaerobic glycolysis, which is highest during the ovulatory phase and falls somewhat in this post-ovulatory period. The aerobic glycolysis is always low, and the oxygen consumption remains fairly constant throughout the cycle.[58] These results on human endometrium cannot be compared with most of the data reported for oxygen consumption and glycolysis in uteri of other mammals,[59] since most of the other mammalian studies utilized sections of whole uteri, including both epithelium and musculature. The endometrium and myometrium, having such different functions *in vivo*, could be expected to contribute quite differently to the total metabolism of the uterus.

The cyclicly changing metabolic requirements of the human endometrium have been reflected also in measurements made by quite a different technique, that of tissue culture.[60] This has provided the perhaps significant information that endometrium requires a high oxygen tension for normal survival during its phase of growth and proliferation under the influence of estrogen. Endometrium can survive equally well anaerobically or at high oxygen tensions under the influence of progesterone following ovulation.

It has also been shown by tissue culture that proliferative endometrium survives best at a pH of 7.3–7.6, while secretory endometrium gives a normal picture only between pH 6.7 and 6.9. It should be noted that such a post-ovulatory drop in pH would favor the observed solution of the zona pellucida of the ovum at the time of implantation.[61] The uterus of the rat is known to have a lowered pH at the height of corpus luteum activity.[62]

Experiments on the rat[63] indicate that uterine vitamin C is highest just before implantation would occur and that uterine glutathione is actively utilized at this time in reduction of the vitamin C. Vitamin C appears to inhibit blastocyst growth without inhibiting glandular proliferation, while glutathione seems to stimulate both of these processes. Whether this relationship exists also in the human is not known, although vitamin C has been demonstrated in human endometrium.[64] Of course, there is precedent for expecting dissimilar roles of vitamins in reproduction of different species. For example, vitamin E deficiency in the rat produces a brown lipoid pigmentation of the myometrium and resorption of the fetus. No evidence for such phenomena, or even a similar vitamin E deficiency, has been found in the human, and treatment of threatened abortion with vitamin E has been disappointing.

Work on the guinea pig[65] strongly suggests that in the implantation process in this species at least, proteolytic enzymes are involved in the erosion of the endometrium observed to precede or coincide with the decidual response of the maternal organism to the fertilized ovum. Erosion preceding the decidual reaction is observed in the monkey also. The many species differences in these processes will necessitate further specific studies of proteolytic activity, however, before conclusions can be drawn on the more general occurrence of this proteolytic phenomenon.

If fertilization and implantation do not occur, the endometrium goes through its characteristic stage of regression. The stimulus for this regression seems to be the withdrawal of estrogen and progesterone as the degenerating corpus luteum ceases production of these hormones. Marked vasoconstriction of the uterine blood vessels follows and is an immediate precursor of menstruation. During the late pre-menstrual and menstrual phases, a substance having vasoconstrictor and fibrinolytic properties appears in the endometrium and has been extracted and partially purified from the euglobulin fraction of the proteins. The detection of this substance, termed "menstrual toxin" because of its toxic effects on rats, points to probable chemical steps connecting the hormone withdrawal with actual shedding of the endometrium.[66, 67]

No attempt will be made here to discuss fully the biochemical studies of the uterine musculature. However, in view of the definite changes in rhythmic contractions which have been noted during the menstrual cycle, some mention should be made of the energy metabolism of this portion which constitutes the bulk of the human uterus. Qualitatively, the same phosphate energy system in operation in the contractions of other musculature of the body, seems to be functional here. Quantitatively, however, the components of the system do show some differences from striated muscle, for example. (See bibliographical reference 68 for detailed discussion.)

The report of the high concentration of peptidases found in human uterus, including a specific dipeptidase for hydrolyzing glycylglycine,[69] may also be of some interest in regard to protein metabolism.

Even from the incomplete evidence at hand, it may well be concluded that one of the principal chemical functions of the female reproductive tract is the nutrition of the sperm and ovum, with final emphasis on a fertilized ovum which is to be carried through pregnancy, and that each section of the tract seems well prepared to carry out this function in the normal individual. Any attempt at the control of conception must recognize the physiological emphasis on success of conception. Increasing knowledge of the biochemistry of the reproductive system should, however, continue to present new possibilities on likely sites and mechanisms of such control. So far, the emphasis has been on inhibition of spermatozoal metabolism at the vaginal level. The blocking of essential responses in the female at uterine or ovarian levels, for example, will require further knowledge of the biochemical reactions which are unique to the female reproductive tract or of more ubiquitous enzymes which are functioning uniquely in these reproductive tissues. The finding that the progestational phase of endometrial development necessary for implantation can be inhibited in the mouse and rabbit by the folic acid analogue, aminopterin,[70] may be a start in this direction.

There does seem to be a biochemical basis, therefore, for hope that the recent prediction of Dr. James B. Conant, concerning an effective, orally administered means of conception control, can be realized.

By actual measurement, the amount of mucous secretion which can be aspirated from the cervix at one time is often increased more than 1,000 per cent during the ovulatory phase.[10] The water content rises from about 92 per cent to close to 99 per cent.[11] Experiments indicate further that this is by no means a completely passive fluid medium through which spermatozoa can always ascend easily, but is instead a complex rheological system in which qualities of *spinnbarkeit* and flow elasticity vary during different phases of the menstrual cycle and may impede, or aid, the forward movement of spermatozoa within it.[12] Viscosity of the mucus, regarded as resistance to flow, declines sharply during the ovulatory phase.[13] A complex polysaccharide, which appears to be associated with the viscosity of the mucus, has been identified in the secretion, and its concentration also has been shown to decline markedly in the ovulatory phase. From chromatographic studies, this neutral mucopolysaccharide is composed of galactose, fucose, and hexosamine.[14] Quantitative determinations by spectrophotometric methods have also recently been reported for the ovulatory phase on its components.[15]

Sperm migration through cervical mucus has most successfully been observed *in vitro* in capillary tubes.[16] While the scanty, thick mucus of the pre-ovulatory and post-ovulatory phases appears to be almost impenetrable to spermatozoa, the abundant, runny mucus of the ovulatory phase has been shown to be easily negotiable by the sperm at a rate up to 3–5 mm. per minute[13] and to support their motility for as long as 72 hours.[17] *In vitro* observations on penetrability admittedly may not duplicate behavior *in vivo*. The results are nevertheless suggestive of the existence of some relationship between the pronounced cyclic changes observed in the mucus and the ability of the spermatozoa to pass successfully through this secretion.

There is the intriguing possibility that other chemical changes, in addition to those associated principally with the physical state of the mucus, may also have a role in this cyclic penetrability by spermatozoa. Further investigations of the chemical constituents of the secretion which would appear to be of importance to the sperm have thus been stimulated. While all of the constituents so far examined have exhibited some cyclic variation, none of them alone has shown a variation seeming to favor penetrability during the ovulatory phase above the other phases. The studies, however, have provided considerable information on the cervical environment through which the sperm must pass.

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Discussion of Paper by Doctors Pommerenke and Breckenridge

Doctor Carl G. Hartman, *Ortho Research Foundation, Raritan, N. J.:* Why do we study the biochemistry of the reproductive process? I am reminded of a statement of John Hammond of Cambridge, England, at a Conference on Contraceptive Methods held at Cambridge April 17 and 19, 1931. Dr. Hammond is a biologist, not a physician, and works entirely with laboratory and farm animals. He stated on that occasion that he had devoted most of his life and researches to the cure of sterility, but he found that much of the subject matter of his researches was equally applicable to the problems of contraception and to problems of sterility.

Let me give one example. To date, no one has been able to bring about test-tube fertilization of the mammalian egg, *i.e.*, the union of egg and sperm, if we except Pincus's questionable single case. In numerous studies with mouse, rat and rabbit eggs, every effort was made to provide a chemically favorable medium for the egg and the sperms, but a factor was lacking. This factor has now been found inherent in the lining of the tube where fertilization normally takes place. Add this factor and, under the new phase microscope, you can see the sperm enter the egg and follow its behavior to the final marriage of the paternal and the maternal chromosomes.

As indicated by Breckenridge, the muscular coat of the genital tract is of great importance, in the transport of egg and sperm, for example. The chemistry of the muscle fibers and their ever-changing behavior and response to nervous and hormonal stimuli is being studied with renewed interest.

Thus new light will be shed on causes of sterility and methods worked out for its cure. Moreover, details of the reproductive process will be discovered permitting the chain of events to be broken and pregnancy avoided. Basic principles must be discovered before practical methods can be developed for reducing the rate of reproduction as well as salvaging barren couples who desperately desire offspring.

BIOCHEMISTRY OF THE MALE GENITAL TRACT

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If one excludes the hormone production of the testes, the biochemistry of the human male genital tract is essentially that of the ejaculate. This statement is based on the assumption that the secretions of the male accessory glands are formed for, and excreted primarily into, the ejaculate, a premise which may not be entirely true. The seminal fluid is a highly complex chemical medium, too complex to be considered as a mere fluid medium essential to the transfer of the spermatozoa from the male genital tract to the female. There is no evidence, on the other hand, that the prostate or seminal vesicle has an endocrine function or that they are organs of internal secretion in the sense that they produce secretory products having a profound effect on the entire organism. It is possible that the prostate, in its relatively high production of phosphatases, may play some role in the body economy, *e.g.*, bone formation, but since the prostate is absent in certain mammals, and the female prostate, when present, is vestigial and probably non-functional, it is safe to assume on present evidence that the main purpose of the male accessory glands is to form a chemical medium to ensure the transport of spermatozoa from the male to the female.

Since the purpose of this paper in this monograph is the consideration of the chemistry of the male genital tract in terms of reproduction, this discussion shall be directed to that end.

Testes. The chief biochemical function of the testis is to provide the androgenic hormone, the secretion of which is essential to the maintenance of the accessory glands which form the secretions comprising the ejaculate. The cellular contribution of the testis, the spermatozoa, is only a small portion of the ejaculate proper in most cases, and it is doubtful that the testicle and epididymis furnish any more fluid to the spermatozoa than is necessary for their transport from the immediate vicinity of the germinal epithelium to the ampulla of the ductus deferens. Actually, we know little about the kinetics of the transport of spermatozoa from the lumen of the seminiferous tubules to the main portion of the ejaculate. Present evidence shows, in the human at least, that spermatozoa, once detached from the cytoplasm of the Sertoli cells, are swept rapidly from the seminiferous tubules, through the straight ducts, the cavernous rete testes and the efferent ducts into the epididymis. Relatively few spermatozoa are found free in the tubules or in the duct system prior to the epididymis. All the evidence relating to this portion of spermatozoa transport points to a passive participation by the spermatozoa, in that they show no motile activity. Their transport must be facilitated in a fluid medium, the chemistry of which is unknown at this time.

Massing of spermatozoa is seen first in the epididymis and it is at this point in the duct system that we obtain objective information on the chemical nature of the fluid bathing the cells. At that, the information is scant and indirect. Huggins and Johnson[5] have analysed spermatocoele fluid which contained spermatozoa and have shown that the NaCl content is within measurable isosmotic limits (0.71 to 0.86 per cent). The specific gravity is low (1.002–1.009) and there is a total absence of acid soluble phosphorus. Only a negligible amount of reducing substances was present, and I can confirm that no sugar is present.[15] We must consider the epididymis a most important link in the duct system, however, and attribute greater significance to the fluid bathing the cells in this environment than is obvious from the scanty evidence available on its chemistry. All the evidence to date points (1) to the epididymis as the storage point for the spermatozoa, and (2), in all probability, as an organ in which further maturation, or ripening, takes place. In the guinea pig, Young[18] has demonstrated that if the epididymis is separated from the testicle and the animal is allowed to breed thereafter, spermatozoa will be present in the ejaculate for several weeks, the animal remaining fertile during that period. The same author has shown that epididymal spermatozoa can produce conception but that sperm obtained from the tail of the epididymis have a higher fertilizing capacity than those taken from the head. In the bull, Zittle and Henle[4] have found marked differences in the metabolic properties of epididymal sperm as compared to those expelled in the ejaculate and suggest that part of the "ripening" process of the sperm in their passage through the epididymis entails a change in function of their enzyme systems. Lardy[10] has not been able to confirm this work but adds new evidence that a "metabolic (respiratory) stimulator" is brought to bear upon the spermatozoa via epididymal secretions. In general, therefore, it is thought that the epididymis is much more than merely a storehouse or a means of transit for the spermatozoa but makes a definite physiological contribution, by secretory means or otherwise, to the economy of the sperm in their slow passage through that organ. My feeling is that our knowledge of the epididymis as an organ is rudimentary and that intensive studies of its function will furnish a vast amount of information. Actually, our total fund of data regarding the kinetics and physiology of sperm transport from the germinal epithelium to the ampulla of the ductus deferens is slim.

Prostate. The work of Huggins and his co-workers[7] has done much to clarify our knowledge of the chemistry of prostatic secretions. One must differentiate between "resting" and "active" (stimulated) secretions. The bulk of chemical evidence in the human is derived from the "resting" secretion. Huggins has calculated that, in man, the latter represents from 0.5 to 2.0 cc per day. We do not propose at this time to itemize all the chemical constituents of prostatic fluid. I would rather refer those interested to the papers of Goldblatt[2] and of Huggins[8] and confine myself to selected data which I consider of importance in relation to the total ejaculate.

One of the characteristics of human seminal fluid is the high concentration of phosphatases. Kutscher and Wolberg[9] noted that the phosphatase activity of urine was much higher in the male and further work by them showed that, of all the body fluids, seminal fluid was by far the richest in this enzyme. Of the accessory glands, the prostate seems to be the sole source of the enzyme known as "acid" phosphatase because it shows its optimum activity at acid pH. The acid phophatase comprises the bulk of phosphatase present in semen, although an alkaline phosphatase in low concentration has been found, its distribution being rather general in the accessory glands. Gutman and Gutman[3] have shown that the level of acid phosphatase is low in infancy, but shows a marked increase in the years of puberty. It may thus be considered as a secondary characteristic in the male. Huggins[8] has used the level of acid phosphatase in the blood of patients with cancer of the prostate as an indicator of metastases or regression of the growth in that gland. Just what the contribution of this enzyme is to the physiologic nature of the total ejaculate is a matter of considerable conjecture. Mann and Mann[19] in a review of this field, point out that the concentration of choline in human semen is so high that its presence has been used in forensic medicine for the detection of semen. The concentration of free choline in freshly-ejaculated semen is very low, however, increasing rapidly on storage. Obviously, there is a precursor of choline and this has been shown to be, in all probability, choline glycero-phosphate. The source of this substance is speculative, but Huggins and Johnson[5] have shown that most of the phosphorus of human semen is derived from the seminal vesicles. Lundquist,[11] who has shown that the "acid" phosphatase from the prostate dephosphorylates phosphorylcholine, believes that phosphorylcholine is formed in the seminal vesicles and that the dephosphorylation only takes place when the vesicular and prostatic secretions unite at the time of ejaculation.

Generally speaking, the presence of the phosphatases and of the various phophorylated compounds in semen have not been related to any function. For example, certain of the phosphatases and phosphorous esters have been studied in relation to the metabolism and motility of human spermatozoa,[17] and no particular relationship has been found. Indeed, as will be shown later in this paper, human spermatozoa require remarkably few chemical substances, organic or inorganic, in their environment to initiate and sustain their vigorous motile activity.

Another chemical constituent of prominence in human semen is citric acid, not found often in body fluids. Its presence has been detected in the semen of most of the higher mammals.[19] In man, the chief source is the prostate, but it is found in the other accessory glands in most other mammals. As in the case of the other substances mentioned here, the role of citric acid is obscure. Mann and Mann[19] have shown that it disappears after castration and re-appears upon injection of androgens in castrated animals. It is thus a secondary sex characteristic. It does not have any obvious nutrient role in the metabolic economy of the spermatozoa. There is a suggestion that it is connected with the coagulation and liquefaction of semen, a subject which is discussed below.

Ascorbic acid levels in human blood plasma depend greatly on the intake but a minimal normal level is considered to be in the region of 1 to 1.4 mgs/100 cc. When it is considered that it reaches an average concentration of around 13 mgs/100 cc[1] in human semen, it is obvious that this substance either is manufactured *de novo* by the male accessory glands or is concentrated by them. Berg *et al.*[1] have found the highest concentrations in seminal vesicle fluid with only very small amounts in prostatic and spermatocele fluids. A further amplification of the seminal vesicle as the chief source of vitamin C is found in the fact that in the dog, an animal without seminal vesicles, semen ascorbic acid is at plasma level. A relationship of ascorbic acid levels has been suggested but no obvious connection determined. Ascorbic acid therapy was reported to be of value in infertile bulls but this work has not been substantiated, nor has any relationship to human fertility been observed. We must consider, therefore, that the persistence of high levels of ascorbic acid in human semen, while highly interesting, is not functionally informative.

The presence of large amounts of reducing sugars in human semen has long been known. The concentration range is anywhere between 60 mgs per cent and 800 mgs per cent, the mean value being in the neighborhood of 300 mgs per cent. When it is remembered that the normal range in blood plasma is 80–120 mgs per cent, it will be seen that sugar is concentrated in the accessory glands. Until a few years ago, this sugar was thought to be glucose although an obscure piece of research in a Japanese scientific journal had shown it to be fructose. In 1945, Mann[18] announced that fructose was the major part of the reducing substance of semen and furnished positive proof by the isolation and crystallization of fructose from the semen of many mammals, including man. The fructose is present in free form. It had already been demonstrated by several observers that the main source of the reducing sugar was the seminal vesicle, very little being found in the prostatic and testicular fluids. Another source has been located in the ampullar glands but this is not surprising, in view of the close proximity of the ampulla to the ductus deferens to the vesicle, and the similarities in histologic structure of the two bodies.

The occurrence of a high concentration of a fermentable sugar which can be, and is, utilized by human spermatozoa for the purpose of obtaining energy for motility comprises the first obvious functional relationship of a chemical substance in semen. The evidence for this relationship is reasonably conclusive and runs along the following lines. There is general agreement that the spermatozoa show no motile activity in their passage through the duct system, at least until they reach the ampulla of the ductus deferens (we shall present evidence that motile activity may be attained at this point). In the human, the ejaculated spermatozoa are dependent entirely on a utilizable sugar for the maintenance of motile activity. When deprived of this sugar, motility ceases but can be re-activated by the addition to their environment of the appropriate sugar.[13] In the fresh ejaculate, examined immediately after ejaculation, motile activity as a rule is quite feeble. Maximal motile activity is attained within a few minutes, however, sooner in some individuals than in others. Since the spermatozoa seem dependent on sugar for the initiation of motility, and since no sugar has been detected in their environmental media prior to ejaculation, it is generally assumed that they cannot attain motile activity until they reach the main body of the ejaculate. Analysis of the orderly nature of the ejaculatory process throws further light on this line of reasoning. Based on chemical analysis, the first portion (first one-third) of the ejaculate originates almost entirely in the prostate. Part of this secretion must be designated as "resting," though almost certainly, most of it is "stimulated," in the sense that pre-coital sexual excitement must induce a liberal flow. Huggins and Neal[6] have shown that the "stimulated" flow may be as much as 20 times that of the "resting," in the dog. In this first one-third of the ejaculate, too, nearly two-thirds of the total spermatozoa expelled are found, in addition to a high concentration per unit volume of lactic acid.[15] The remaining two-thirds of the ejaculate is comprised of the bulk of the vesicular fluid, as evidenced by the relatively high concentration in the ejaculate of substances common to the seminal vesicle, *i.e.*, fructose, citric acid. Few spermatozoa are found in this portion. In the light of this evidence, we can visualize the ejaculatory process as one in which the release of secretory and cellular products from the various portions of the male genital tract is by no means simultaneous. "Resting" secretion of the prostate undoubtedly is present in the urethra prior to ejaculation and this is augmented by "stimulated" secretion during pre-coital stimulation. Whether there is further augmentation by an expelling or "squeezing-out" of further prostatic secretion during the initial spasm of ejaculation is debatable, but, certainly, the bulk of the total contribution of the prostate is in the initial portion of the ejaculate. The presence of the majority of the spermatozoa in this portion is direct evidence that they necessarily were massed close to the urethra just prior to ejaculation. The only logical site for this "massing" is in the ampullae of the *vasa deferentia.* Further evidence in substantiation of this line of thought is the concentration of lactic acid in the initial portion of the ejaculate. This acid, expelled with the spermatozoa, necessarily comes from the environment of these cells. We know that lactic acid is the metabolic end-point of the breakdown of sugar by human spermatozoa. We have demonstrated, furthermore, that, in the ejaculates of azoospermic men, the disproportion in the concentrations of lactic acid in the first and second portions disappears, leaving an equal distribution of lactate, no matter which portion of the ejaculate is analyzed. Therefore, the initial spasm of ejaculation must comprise, in addition to the prostatic contribution, a contraction of the ampullae of the *vasa deferentia*, forcing the spermatozoa massed at that point, into the urethra.

The expelling of the seminal vesicle contents must follow this order of precedence inasmuch as we find (chemically) its secretions in the second portion of the ejaculate. If any further evidence is required that the seminal vesicles are not "storehouses" for the spermatozoa, the presence of few spermatozoa in their contribution to the total ejaculate is decisive. This line of thought, based on sound evidence, suggests that ejaculation, in point of time, is a three-stage process, namely, (1) expelling of prostatic fluids; (2) contraction of the ampullae and projection of the spermatozoa into the urethra; and (3) liberation of the contents of the seminal vesicles. Undoubtedly, there is some overlapping, but it seems certain that the bulk of the spermatozoa do not come in contact with the secretions of the seminal vesicles until ejaculation takes place. Fructose, a substrate which furnishes a ready source of energy for motility, is in these secretions. It is not surprising, then, to find that the spermatozoa are only feebly active immediately after ejaculation. If one argues on a chemical basis alone, and limits the source of utilizable sugar to the seminal vesicles, the argument presented above is sound. We, have shown already, however, that a considerable amount of lactic acid has been formed by the spermatozoa prior to ejaculation. The evidence to date is that human spermatozoa can form lactic acid from utilizable sugars, not from amino acids, fats or any other such obvious source. The conclusion is that, prior to ejaculation, the spermatozoa have reached a source of motility substrate (sugar), are breaking it down, and that motility may have been initiated prior to ejaculation. If one further accepts the evidence that the spermatozoa show no motile activity in the epididymis, they must pick up the substrate after leaving the epididymis, before reaching the urethra. The ampulla is the logical site for this "pick-up," not only geographically, but in terms of time. Since the spermatozoa may take weeks to reach the ejaculate, after leaving the germinal epithelium, early initiation of motile activity would be suicidal. Teleology and objective evidence suggests late initiation of motility by virtue of accessibility of substrate (sugar), either just prior to ejaculation in the ampullae or during the ejaculatory process, upon the mixing of the spermatozoa with the secretions of the seminal vesicles.

If the position is taken that motility is initiated in the ampullae, why do the spermatozoa show such feeble motile activity in the fresh ejaculate? There are purely physical reasons why this should be so and they are inherent in another important aspect of the chemistry of the male genital tract, considered below.

The importance of fructose or any utilizable sugar as a component of semen is established. This sugar is rarely found in the body fluids of the adult and why it should be formed in such quantity by the seminal vesicle is hard to understand. The spermatozoa use glucose with equal facility and, indeed, will selectively metabolise glucose in the presence of fructose; nor is there any apparent necessity for the high concentrations of fructose found. Under experimental conditions, a concentration around 10–20 mgs per cent will initiate and sustain motile activity.[12] Furthermore, there is no relationship between the sugar concentration of semen and fertility.[15] A common feature of the semen of infertile men is poor motile activity (complete necrospermia is rarely found) but a seminal sugar deficiency is never the answer to this problem.

The Nature of the Coagulation and Liquefaction of the Human Ejaculate. We do not propose to review in this monograph the almost universal phenomenon of coagulation of semen in the mammal. This subject has been considered recently in detail by Mann and Mann.[19] Fresh human semen is coagulated but liquefaction takes place rapidly (within 15 minutes) at room temperature. The degree of coagulation is variable in different individuals and, in certain cases, the semen viscosity may remain high indefinitely. Huggins and Neal[6] have made the most comprehensive study of the coagulation process and observed that liquefaction is an enzymic reaction facilitated by a proteolytic enzyme in the prostatic secretion. They designated this substance as a "fibrinolysin" similar to that found in hemolytic streptococci. It is not the same, however, nor is it related to the fibrinolytic enzyme of blood. Huggins and Neal[6] also have found fibrinogen and thromboplastin in semen prior to liquefaction, but not afterwards. They consider that seminal clotting resembles blood clotting but that it may not be identical. Morphologically, the semen clot resembles fibrin formation. The presence of an active fibrinolytic agent in the semen would readily explain liquefaction, particularly if fibrin were the cause of the clot.

The necessity for the *bouchon vaginal*, or vaginal plug, in the lower mammals has never been fully understood, nor is it quite clear why semen coagulation should be necessary in the human. Furthermore, we have no evidence to date of the effect of the vaginal environment on the liquefaction process, that is, whether the latter is hastened or retarded by the relatively high acidity of the vagina. For that matter, we have at hand remarkably little information on the passage of spermatozoa from the seminal pool into the cervical canal. Is it a passive process in the sense that this coagulated semen, with its complement of feebly active spermatozoa, is forced into the cervix at the time of ejaculation, or is it an active one, by virtue of the spermatozoa attaining full motile activity before migrating on their own volition into the cervical canal? I have never seen or heard of a full discussion of this point and it has always seemed to me that there are gaps in our reasoning. For an example, one we have discussed already, the sperm are only feebly motile in the fresh clotted ejaculate, particularly if the clot is a firm one. We have suggested that this poor quality of motility is, in effect, merely the initiation of motility, due to the first meeting of the spermatozoa with a utilizable sugar. We also have postulated, however, that motile activity may be present prior to ejaculation, *i.e.*, in the ampullae.

How can we reconcile these two points of view? We can do so by considering the physical nature of the fresh ejaculate. A firm seminal coagulate effectively binds the spermatozoa in its fibrous mesh so that, even if they were actively motile prior to the formation of the clot, they are immobilized in its meshes. This immobilization can be observed readily in certain fresh semen specimens. We must assume, in the physiological course of events, that the coagulated semen mass is deposited at or near the cervix in intercourse. If the entry of the spermatozoa into the cervix is dependent on the motile activity of the cells, there is necessarily a delay, therefore, of a few minutes before they gain sufficient activity to do so. It is possible that the semen coagulation exerts a protective influence during this time although the necessity for this is by no means obvious. It would seem more logical if the spermatozoa were fully active at the time of ejaculation.

The Buffering Power of Semen. At the time of ejaculation, the pH of human semen is in the physiological range (pH 7.1 to 7.4), but if it is allowed to stand in a test-tube exposed to air, it rapidly becomes alkaline. Readings of pH 9 to 9.5 have been obtained in my laboratory on hours-old semen. This change in pH can be ascribed to loss of CO_2, since a plentiful supply of bicarbonate is found in semen. A drastic pH change of this kind is not likely to take place under *in vivo* conditions, particularly in the acid environment of the vagina. What is more important is that semen is very effectively buffered against acid by the presence in it of relatively enormous amounts of inorganic phosphate,[2] plus a mere physiological concentration of bicarbonate. Thus, the seminal fluid can be most effective in protecting the spermatozoa against the acid environment of the vagina. Human spermatozoa in seminal fluid lose their motility when the pH is lowered to approximately 5.9 by the addition of lactic acid,[14] although motiliy can be restored by raising the pH above 6.2. It would seem essential, therefore, that the spermatozoa, after ejaculation, reach the alkaline cervical canal quickly or be well protected in the vaginal environment. Their protection is the buffering power of the seminal fluid, although it is doubtful if the latter can be maintained effectively for extended periods. It is not surprising that one finds few motile spermatozoa in the vaginal pool two hours after intercourse, whereas motility may be retained up to 72 hours in the cervical canal.

Other Substances Present in Seminal Plasma. The proteins of semen in large part are derived proteins. Huggins *et al.*[7] give figures showing that 60 per cent of seminal proteins pass through cellulose membranes whereas no blood serum proteins pass through. The general belief is that most of the protein substances are proteoses, primary and secondary. Their significance is entirely unknown.

The large amount of spermine phosphate present is apparently derived from the prostate, but its value, apart from its buffering power, is debatable.

Summary. This relatively brief discussion of the biochemistry of the human genital tract has not omitted any item of importance discovered so far. Enough has been given to show that the seminal fluid is chemically complex. It is too complex, as we have said, if its only primary function is transport of the spermatozoa from the male genital tract to the female. We should remember that, under normal conditions, the seminal fluid is not a physiological environment for the spermatozoa for any appreciable length of time. The cells do not reach the body of the ejaculate until ejaculation takes place and, almost immediately, they are deposited close to the point in the female genital tract where they must make their entry. It is true that we have no positive evidence of the speed with which they gain the cervical canal, but most authorities believe that the spermatozoa which eventually reach the Fallopian tubes must pass into the cervix soon after ejaculation. Their stay in the ejaculate, therefore, must be quite brief. Perhaps the time is long enough to allow them to pick up essential substances from the seminal fluid but the identity of these substances, apart from sugar, is a mystery.

Actually, the spermatozoa, from the point of view of motility, survive for long periods, in a relatively simple medium, provided sugar is present.[13] They are capable of withstanding changes in their environment which most body cells cannot. For example, a solution of 1 per cent NaCl and 10 mgs per cent glucose will sustain motility for hours, provided the pH remains constant. Even reducing the toxicity of NaCl to 0.6 per cent may not damage motility severely.[16] One can vary the ionic concentration of K one hundred-fold and not produce any obvious change in motile activity or in the metabolism of the cells. Other ions, too, can be added in high concentration without severe damage to motility. As an academic point, however, their motility is extremely sensitive to very small concentrations of lithium chloride.[16] The presence of fructose in the seminal fluid does not seem to be of any value in the light of present evidence. The spermatozoa use either fructose or glucose equally well in obtaining energy for motility and, indeed, there is some evidence that if they are presented with a choice of these substrates they will use glucose preferentially.

There is no suggestion in any sound data in the literature that prostatic secretions "activate" sperm motility, a concept which has been espoused in older text-books. The only reasonable conclusions we can make at present are that the seminal fluid, comprised of secretions from the accessory glands of the genital system, furnish the fluid medium essential for the transport of the spermatozoa to the female genital tract and that, by virtue of its sugar content and buffering capacity, certain stimulatory and protective effects are conferred upon the spermatozoa.

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Discussion of Paper by Doctor MacLeod

Doctor Carl G. Hartman, *Ortho Research Foundation, Raritan, N. J.:* Study of the physiology of the male has lagged behind that of the female. Perhaps the chief reason is that sterility was considered the fault of the female, until recently, although more studies of barren marriages add a larger percentage of cases in which the ejaculate is found to be defective, not to mention the addition of a small proportion of actual impotence. There has been considerable activity in recent years in the study of the metabolism of the sperm cell and Dr. MacLeod has made notable contributions in this field. It can be seen readily that this approach applies to our subject, because a knowledge of the requirements of the sperm cell will allow us to supply the deficiency to permit conception or withdraw it to render the sperm cell non-functional. In the past, knowledge of this kind has been used in the artificial insemination of cattle, resulting in increased animal production.

One of the most helpful facts in animal and human reproduction is the short survival time of the sperm cell on reaching a favorable environment. Sperms are quiescent in the male tract. The reason for this quiescence is preservation of the sperm. We have attributed this quiescence to a low pH, due to CO_2 engendered when they were packed closely together. According to David Bishop, it now appears more likely that the important factor is low O_2 tension, since they are quiescent at a pH as high as 6.8 in an atmosphere of low O_2. Dr. Bishop constructed an oxygen electrode sufficiently fine for insertion in the slender vas deferens of the rabbit. He found the O_2 tension below that of venous blood.

Dr. MacLeod's new observations on the coagulation of freshly ejaculated semen, with concomitant low motility of the contained sperms, are of interest to all of us who are working in this field. It is a matter of enzyme action. The enzyme involved seems to be a non-specific one, since Gertrude von Wagenen found that the contents of the appropriate lobe of the monkey prostate will coagulate the secretion of the rat seminal vesicle and the "Walker's gland" of the rat will coagulate the secretion of the monkey's seminal vesicles. The gland responsible for the enzyme mentioned here has been identified in rodents and in the monkey. No such lobe of the prostate has been described so far in the human prostate.

A CRITICAL STUDY OF METHODS OF MEASURING SPERMICIDAL ACTION

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Historical Introduction. It is now almost one hundred years since Kölliker[33] published the first investigation of the effects of chemical agents on the motility of sperm. While this was an auspicious beginning, subsequent progress was slow, perhaps because the world was not ready to adapt such findings to practical use in contraception. Baker[7] has aptly stated that "the history of contraception has been the history of customs rather than the history of science." Fortunately, in the light of events of recent years, this is no longer true.

Considering the state of knowledge of those years, Kölliker[33] applied some brilliant tests to sperm. For example, while he did not recognize the phenomenon by name, he showed the effect of tonicity on the sperm of bull, horse, dog and rabbit. He found that pure water cannot be used to dilute semen, since it acts as a "poison." Although he did not develop a standard method for making his tests, he nevertheless demonstrated that acids immobilize sperm and alkalis reactivate them, that alkaloids have some spermicidal powers, and that some biological fluids themselves have marked action on sperm.

Incredibly enough, fifty years elapsed until the next major work. The year 1907 found Günther[31] investigating the effect of many substances on sperm, and using a standard system of one part semen to nine parts isotonic saline containing the spermicide. His end point was the immobilization of the sperm, and although his work corroborated Kölliker's, the scope of substances he tested was far greater. We are indebted to Günther for the first true spermicidal test, and for our knowledge of the spermicidal power of the hydroquinones and other reducing agents.

A long interval again ensued until scientific interest focused once more on spermatozoal response to chemical environment. In 1931, Gellhorn,[28] working with guinea pig sperm in isotonic solutions of salts, showed the order of toxicity of some anions and cations. Indeed, certain salts apparently prolonged the life of sperm above their normal span in sodium chloride solutions alone. Alvarez[1] has also made a similar study of the effects of some of these ions on the sperm cell.

The careful investigations of Baker and his associates had their beginnings in 1928, and culminated in the volume "The Chemical Control of Conception."[7] These workers not only established methods for the testing of pure spermicides but also undertook the spermicidal examination of contraceptive preparations.[2–9, 11–14] We shall discuss some of these at a later point. During these same years, Voge[47–50] was conducting a critical appraisal of the contraceptive industry and methodology; and his work ultimately appeared in the volume "The Chemistry and Physics of Contraceptives."[47] At the same time Gulland and Mead[29–30] were expanding the investigations into the spermicidal activity of quinones.

The next few years were characterized by the attempt to establish better tests for spermicides and contraceptive materials. In 1940, Brown and Gamble[17] published a method of spermicidal testing, which was followed by a series of pioneering periodical reports on the efficiency of various commercial preparations.[15–18, 20, 21, 27] The following year Sander and Cramer[42] published on a spermicidal test and also evaluated the efficiency of complete contraceptive preparations.

About the time of Gellhorn's publication in 1931, the group with which I have been associated for the past ten years began systematic investigation into chemical contraception. During these years, thousands of tests have been made by various methods on pure chemicals and on contraceptive formulations. Our file on spermicidal results contains information on about one thousand agents, and this wealth of data has permitted a careful analysis of the various tests under a variety of conditions.

When we consider "spermicidal" substances, which may seem a rather narrow field at first thought, we know that it is not the contraceptive investigator alone who is interested. The reaction of the germ cells to various materials in toxic and non-toxic doses of chemicals is a matter of concern to workers in many other fields: the biochemist and biophysicist, the nutritionist, and the toxicologist.

The results of spermicidal tests have a particular interest to those investigators concerned with the metabolism of sperm. They, in turn, contribute from their work reciprocal information important to the investigator of spermicides. For example, we know through MacLeod[37] of the sulfhydryl sensitivity of sperm; through Ivanov,[32] of the action of metabolic poisons such as iodoacetate and cyanide on the motility of sperm; and through Lardy and Phillips,[34] of the toxicity of arsenite, selenite, and other substances for sperm. There are so many other such contributors that all cannot be listed here. One phase that has been exploited only slightly is the actual effect of some spermicides on the metabolism of sperm.

This very brief history, which is by no means all inclusive, serves to emphasize one major point: the science of spermicidal measurement is still a young one, but it is destined to mature rapidly as a specialized branch of investigation.

Problems and Methods of Spermicidal Testing. Before continuing, we must state our awareness that two distinct problems are involved in this science. There is considerable difference between testing a pure chemical as a spermicide, and testing the efficacy of a contraceptive formulation. Physically and chemically, the conditions are different, and it is unlikely that the same test which permits rapid screening of potentially spermicidal compounds in the laboratory is equally suited to testing the spermicidal potency of a finished product.

For this reason, the role of the laboratory in the evolution of a properly composed chemical contraceptive has many facets. Assuming that a substance has been found to have ideal spermicidal powers—swift, efficient, non-toxic, non-irritating, available, reproducible, and inexpensive—it is the job of the testing department to follow such a chemical through the many types of compositions which may be designed for it by the pharmaceutical staff. This department checks spermicidal efficiency through pilot plant batches, through the clinical testing program, and finally keeps a close check on each production batch. It must, at the same time, be aware of new developments in the field, and be able to evaluate them.

Faced with these problems, the investigator must decide what tests he shall use, and under what specific conditions. For the final, or commercial, formulation, the test should simulate actual physiologic conditions as closely as possible. Although the screening of spermicidal compounds presents its own problem, the choice of tests in both cases, however, depends upon a critical analysis of certain conditions; among these are the criteria of activity, species, control of the semen specimen, temperature, diluents, degree of dilution, amounts of semen, method of mixing, and reproducibility.

Before considering these points in detail, let us briefly review four types of spermicidal tests in general use. The Brown-Gamble[17] test, which has been adopted by the American Medical Association as a requirement for inclusion of preparations in their New and Non-Official Remedies,[40] requires as little as 0.04 ml semen. This is measured and mixed with an equal volume of a contraceptive diluted 1:4 with saline, by means of a special apparatus, and the survival time of sperm in this mixture noted.

The Sander-Cramer[42] method uses 0.2 ml semen against 1.0 ml of diluted contraceptive, mixed in a centrifuge tube. Its aim is to determine the greatest dilution of spermicide which can still kill all sperm instantaneously.

The Baker group in England has given us several types of tests. One of these,[12] a general test for measuring the relative efficacy of spermicides, requires 0.3 ml semen or sperm suspension versus various dilutions of spermicides in equal volume. The motility of sperm is examined at 5 and 30 minutes, and again, in the event of immobilization, after diluting with an alkaline "revivification" fluid. Still another test was designed by Baker *et al.*[12] as a measure of the ability of spermicides to diffuse out of a vehicle. The composition is mixed with an "artificial vaginal fluid" and 1.25 ml semen added. The survival time of the sperm is measured and they are also later subjected to alkaline medium to insure that they are dead.

Choice of Species. Because of the frequent difficulty in obtaining human semen, the question arises whether the semen of other species may be substituted for it in spermicidal tests. Interesting correlations have been drawn concerning the relative response of various types of sperm to classes of spermicidal substances. Kölliker,[33] in 1856, had already demonstrated the similarity of bull, dog and rabbit sperm reactions to sugar solutions and alkaloids. His data have more historical than absolute value, since the conditions of the experiments are not well known, and do not include the human. Nevertheless, other fairly good correlations have been found. Günther[31] made a multitude of such correlations in his studies of "Spermiengifte," covering a wide range of substances, but still exclusive of the human. Baker's[6] contribution has, of course, become classic and his correlation between guinea pig and human sperm appears very close indeed. In a study of the comparative activities of spermicides on human, rabbit and guinea pig sperm made by us (FIGURE 1), it is noted that, while the human semen seems more resistant in general, the more efficient spermicides show up better across all species. In an extended study of 31 phenolic derivatives (FIGURE 2), we have found this to be generally true, although subject to some variation, as shown in the scatter diagram. The general feeling is that while, in the absence of human semen, it may be practicable to use the sperm of other species for rapid screening technics, nevertheless the final selection of the best spermicide must be made by use of human semen. Furthermore, for the testing of complex formulations, human semen is regarded as essential.

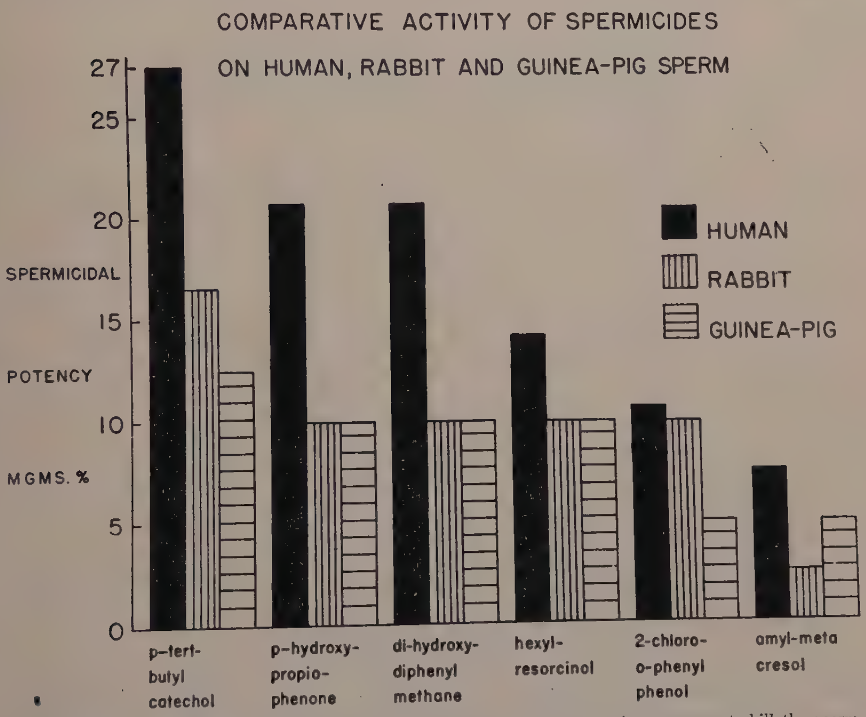

FIGURE 1. Spermicidal potency is expressed in mgms. per cent concentration necessary to kill the sperm instantaneously. Thus, the shorter the bar, the greater is the spermicidal power of the compound.

Control of the Sample. The tremendous variations in individual semen samples is reflected in the variations in spermicidal determinations. This point has been adequately represented by Brown and Gamble[19] and our experience during the years has corroborated it. It follows that the spermicidal time will also vary with the donor.[27] Since a "weak" semen will give erroneous results, several methods[10, 17, 35, 38] have been suggested to weed out the weaker samples. These are described in TABLE 1.

Specimens that do not measure up to the standard in any method are not used in spermicidal tests. Yet, if by the now generally adopted phthallate test the weaker samples are omitted, the other extreme must also be considered, namely: the "resistant" sperm. Tynen[46] calls attention to this problem, while Brown and Gamble[17] and Levenstein[35] claim "resistance" is widely variant among donors. Baker *et al.*[12] note that resistance is probably not correlated with numbers of sperm, and some donors are especially resistant, except to acids.

Because we felt, as did Gamble,[26] that the action of phthallate in a "control" procedure could not always be compared with the action of finished preparations, we subjected specimens from some 20 donors to tests with a specially prepared formula. TABLE 2 is a representative section of the results. Donor AR was always resistant to this formula, while it can be seen that BR was inconsistent. Donor C invariably gave the spermicidal time representative of other donors for this preparation. We have made various tests to determine the source of this resistance. In TABLE 2, it is obvious that it does not reside in the actual numbers of sperm, but rather may be a function of the buffering capacity of the semen. This is further supported by the evidence that the resistance lies in the seminal plasma, since washing and resuspending the sperm in saline destroys their resistance.

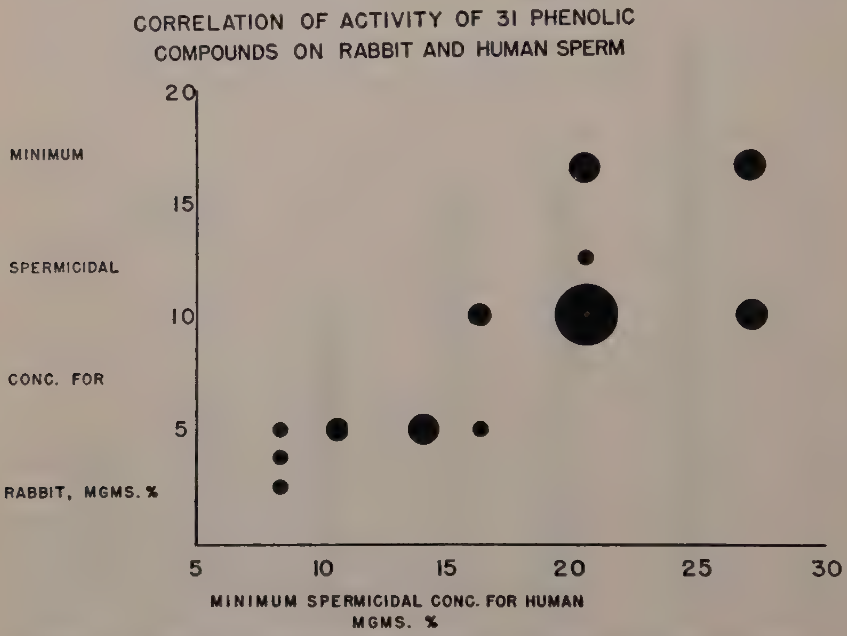

FIGURE 2. The size of the black circle indicates the number of compounds falling on that point. In increasing order of size, the four sizes of circle represent 1, 2, 3, and 10 compounds respectively.

Whatever the nature of resistance, the successful spermicide must be able to kill even the most resistant single spermatozoon. In order to determine the nature of the specimen, control procedures are therefore essential. It has become our practice to run control tests not only against phthallate but also against a "standard" contraceptive formulation.

Temperature of the Tests. Since sperm are subjected to 37°C. temperature before and, indeed, after ejaculation, it would appear logical to subject them in the *in vitro* tests with spermicides at the same temperature. The protagonists of this concept will agree with Weisman[51] that any other temperature is nonphysiologic and misleading. Baker and his associates[7, 12] have used body temperatures in all their tests.

Nevertheless, the complications of temperature control have led many investigators to examine whether it is truly necessary in evaluating relative spermicidal efficiencies. FIGURE 3 is an analysis of data supplied by Brown, Levenstein and Becker[21] which demonstrates that by their test the relative spermicidal efficiency of a series of contraceptive preparations at room temperature is not materially different from results found at 37°C. The results of a considerable number of trials[15, 21] have caused them to suggest that the additional difficulties involved in maintaining the mixtures at 37°C. are not required. This is the opinion voiced also by Günther[31] and by Moench.[39] Shettles[45] and Macias de Torres[36] also took the trouble to make their measurements at body and room temperatures. Unfortunately, there has been little such investigation on pure spermicides, but within limits it ought to be similar, especially since there are no "inert" materials, such as vehicles, to influence the relative results.

TABLE 1
CONTROL OF THE SEMEN SAMPLE "RESISTANCE TESTS"

Method	*Test material*	*Amount of test material*	*Amount of semen*	*Criteria*
Milovanov (1934)......	Sodium chloride, 1%	R	V	R = amt. needed to produce immobilization. Therefore R/V = Resistance Index.
Baker (1939)...........	Quinine bisulfate, 0.25% in 0.9% NaCl	0.3 ml.	0.3 ml.	"Good" specimens still show some motile sperm after 30 minutes.
Brown-Gamble (1940)...	Potassium acid phthallate, 2.8%	A	A	(Equal amounts) Survival time greater than 15 minutes.
Levenstein (1940)......	Sodium lauryl sulfate, 0.2% in 0.9% NaCl	B	B	(Equal amounts) Survival time of 20–60 minutes.

It would seem, then, that the only type of test in which body temperature would be required is one in which the passive diffusion of a spermicide from a vehicle and its mixture with migrating sperm is involved.[35] Such a test is the Baker[12] diffusion test and our own "zone" test to be described later, when both are used on finished preparations. Vehicles vary so widely in physico-chemical characteristics that it may be expected that their "barrier" properties at 37°C. may differ considerably from those at room temperatures.

Diluents. The selection of the diluent is a matter of prime importance in the testing of both pure chemicals and contraceptive formulations. Suggested diluting fluids have been numerous, as seen in TABLE 3. The ideal diluent would, of course, be the mucus found in the vaginal tract, but it is impractical to obtain, and less uniform in constitution. In 1940, Brown and Gamble[17] demonstrated that the choice of any of several diluents did not alter the order of spermicidal potency found for commercial contraceptives.

We will only briefly discuss here the problem of buffered spermicides and also the buffering capacity of semen which, as we have already noted, may be the cause of "resistance" in some specimens. We shall not go into a detailed analysis of a problem which has been so well handled by Emmens and Swyer,[24, 25] Shedlovsky *et al.*[43, 44] Sander,[41] Tynen[46] and others. It is apparent that a vehicle designed to act in acid medium should be well enough buffered to maintain that medium against any seminal plasma buffers,[43] and this is a problem for the compounding specialist. Because of the confusion of suggested diluents for spermicidal tests, and the real possibility of a buffered medium giving misleading results, we have used physiological saline as our major diluent, with the additional check of pH measurements. Where the latter shows such necessity, we may test, as Baker does, for revivification of the sperm by either further dilution or by the addition of an alkaline reagent.

TABLE 2

"RESISTANT" SEMEN (SPERMICIDAL TIME IN MINUTES, S-C METHOD)

	Donor		
	AR	*BR*	*C*
Spermicidal time	30+		1.5
Sperm Count × 10^{-6}	116		110
Spermicidal time	30+	30+	2.0
Sperm count × 10^{-6}	158	132	128
Spermicidal time	30+	1.25	1.50
Sperm count × 10^{-6}	164	136	96
Spermicidal time	30+	1.25	1.25
pH of mixture	6.64	5.85	5.85
Spermicidal time	30+	1.50	
pH of mixture	6.89	5.98	
Spermicidal time		15	1.7
pH of mixture		6.90	6.21
pH of semen		7.68	7.42
Spermicidal time	28		1.50
After washing	.33		.33
Spermicidal time		30+	1.25
After washing		1.50	.33

Degree of Dilution and Volumes Used. Probably even more critical than the diluent itself is the degree of dilution or, indeed, whether any dilution should be made at all. TABLE 4 shows the dilutions of contraceptive material used in the various tests. None of the ratios are the same, although some investigators have planned theirs on the theoretical amounts of vaginal mucus and semen normally present. In no case, however, is the semen treated with such a volume of diluent that it is in danger of being immobilized by dilution alone. The quantities of agent and of semen to be used, however, pose certain important problems. The Brown and Gamble test has the advantage of using very small amounts of both, which permits many tests to be made on the same semen sample. However, since the amounts of contraceptive and semen are so small, the question arises whether, in view of their heterogeneity, representative samples can be drawn. This question, coupled with the mixing difficulties of the method, has led us to examine it for reproducibility. Almost no investigators except the Gamble group have published figures on repeated tests on the same substances with the same semen samples. Some of their data show up to 70 per cent variation in survival time in such experiments,[17] and occasionally wide standard deviations.[20] They report, however, by placing preparations in groups of similar survival times, so that generally there is little change in relative order. We have had similar deviations in our own tests with the Brown and

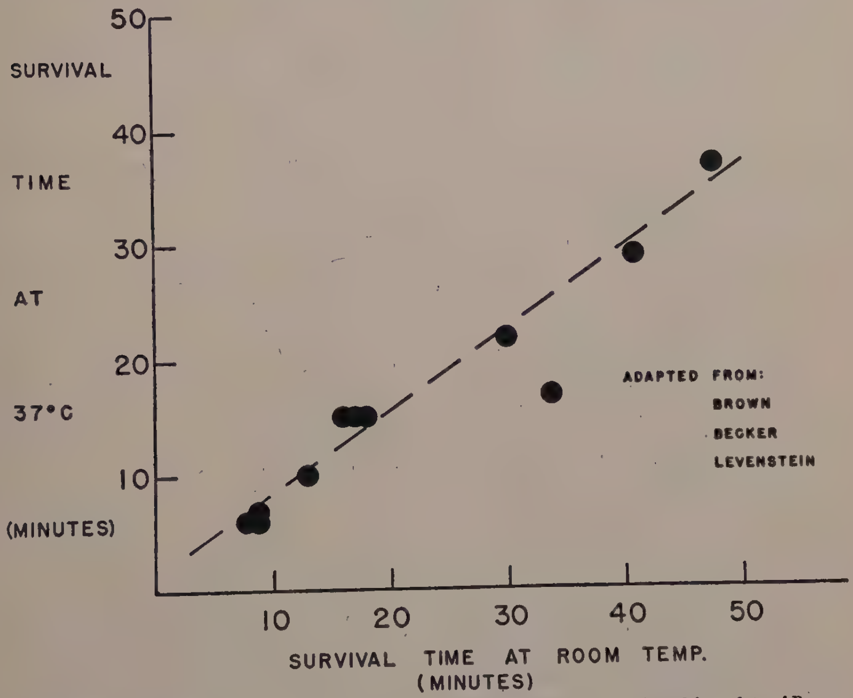

FIGURE 3. Correlation of survival times at room temperature and at 37°C. Plotted from data of Brown, Levenstein and Becker.[21]

TABLE 3
COMPOSITION OF DILUTING AGENTS
(ALL VALUES OF REAGENTS IN GMS., OF FLUIDS IN ML.)*

Name:	*Saline*	*Buffered glucose solution*	*Buffered glucose modified (BGS)*	*Acetate glucose (AGS)*	*Alkaline diluting fluid*	*Artificial vaginal fluid (AVF)*	*Phosphate albumen*	*Albumen-saline*	*Dextrose*
Use:	*General*	*General*	*General*	*"Metals"*	*"Total spermicidal power"*	*"Diffusion test"*	*"Acids"*	*Semen Substitute*	*General*
NaCl	0.85–0.9	0.20	0.20	0.60	0.10			0.063	
KH_2PO_4		0.03	0.01		0.005				
$Na_2HPO_4\ 12H_2O$		0.60	0.60		3.30		.084		
Glucose		3.00	3.00	1.20	1.50				5.00
Sodium acetate				0.13					
Egg-white						10.000	1.600	2.30	
Lactic acid						.042			
NaOH				to pH 8.5					
Water	100	100	100	100	100	1.400	1.400	0.700	100
Developed by	—	Baker[2]	Baker[5]	Baker[5]	Baker[12]	Baker[12, 13]	Baker[7]	Baker[7]	Brown and Gamble[17]
Used by	Sander and Cramer[42]. Becker, Brown, Gamble and Levenstein[15-17, 20, 21]. Voge[47]	Baker[2-4, 7, 8]	Baker[5-7, 9]. Brown and Gamble[17]. Gulland and Mead[29, 30]. Sander and Cramer[41, 42]. Shettles[45]. Voge[47]						Sander and Cramer[42]

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* Baker's "Lactic-salines"[7] and Emmens' buffer types[24] not included here.

Gamble method in spite of repeated trials with most precise technic. We feel that these variations are due both to a statistical difficulty in selecting such a small sample of semen or diluted contraceptive, and to the mixing difficulty as noted by Levenstein.[35]

Few investigators have attempted to get away from dilution entirely. Voge[47] has reported on spermicidal tests using undiluted jelly and semen in ratios of 1:1 or 1:2, with measurement of immobilization time as the end point. In our laboratories, W. C. Mende and V. R. Berliner have developed a "saturation" test in which the criterion is that total amount of semen which can be immobilized by a unit amount of contraceptive agent.

TABLE 4

DEGREE OF DILUTION AND VOLUME OF SEMEN

Test	*Ref.*	*Amount of Agent*	*Amount of Diluent*	*Amount of Semen*	*Ratios*		
					Agent	*Diluent*	*Semen*
Günther	31	variable	9 drops	1 drop	X	: 9	: 1
Baker	4	0.20 dose	0.5 ml.	1 ml.	1	: 2.5	: 5
Baker *et al.*	12	0.25 dose	0.25 ml.	1.25 ml.	1	: 1	: 5
Baker *et al.*	12	0.20 dose	0.30 ml.	0.30 ml.	1	: 1.5	: 1.5
Brown-Gamble	17	0.008 gm. or ml.	0.032 ml.	0.04 ml.	1	: 4	: 5
Sander-Cramer	41	0.20 gm. or ml.	0.80 ml.	0.20 ml.	1	: 4	: 1
M. de Torres	36	0.5–2.0 ml.	0	0.125–0.5 ml.	1	: 0	: 4
Voge	47	1 ml. 0.5 ml.	0 0	1.0 ml. 1.0 ml.	1 1	: 0 : 0	: 1 : 2

The "saturation" test is a measure of the total spermicidal power of a contraceptive. In brief, 0.05 ml of undiluted preparation is deposited in a small tube. Then 0.1 ml of semen is added and mixed thoroughly with the agent for 10 seconds. The sperm are examined at 20 seconds, and if all are dead within the examined sample an additional 0.1 ml semen is added. Mixing, observation and addition are repeated until a sample shows live sperm at 60 seconds.

Thus the total amount of semen which can be handled by a contraceptive agent can be measured. It has become convenient to express this value in volumes of contraceptive initially used. For example, if 0.05 ml of agent is used and 0.3 ml semen inactivated by it, the saturation value is 6.

While the test requires large amounts of semen, its advantages in spot-checking or comparing the total spermicidal value of an undiluted preparation are obvious. For example, FIGURE 4 is a comparison of leading jellies by the 60 second saturation test. In this figure, and others following, A is a synthetic base gel with 1.17 per cent ricinoleic acid and 1.0 per cent of a surface-active agent; B contains 0.05 per cent of an organic mercurial in a vegetable gum base plus 0.3 per cent surface-active agent; C has 0.1 per cent hexylresorcinol and 0.5 per cent ricinoleic acid in a vegetable gum base; D contains 0.02 per cent of an organic mercurial plus 2.0 per cent boric acid in vegetable gum; E is composed of a synthetic base with 1.0 per cent boric acid and 5.0 per cent surface active agent.

Methods of Mixing. Undoubtedly, the most vexing problem in spermicidal testing is the question of mixing semen and spermicide. The very variety of methods indicates the thought which has been given to the problem. Against the bubbling and shaking methods (Baker[2, 3, 12]) may be leveled the argument of inadequate mixing and the incorporation of air. Pipette mixing with a rubber bulb as used by Günther[31] and Sander-Cramer[42] is not always reproducible with "sticky" samples. Mixing on a cover-slip by repeated intake and expulsion as in the Brown-Gamble technique yields variant results. For example, Levenstein[35] has noted that in the Brown and Gamble test "it is thus very difficult to repeat the same type of mixing in different experiments . . . a difficulty often arises when the jelly is quite viscous." His own method, using a hypodermic syringe, is criticized by him on the same basis. Voge[47] has used capillary pipettes or "loopfuls" of agents and semen.

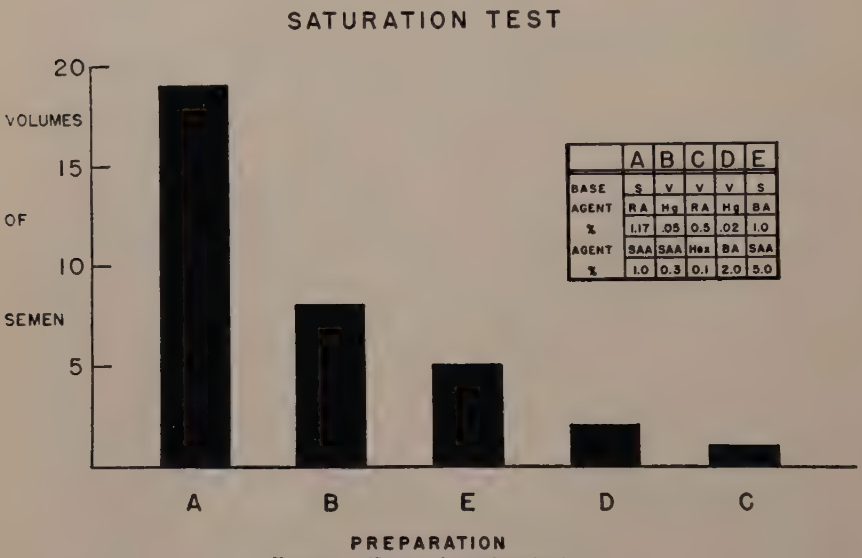


FIGURE 4. (See text for explanation.)

It is particularly difficult to understand the conditions laid down for the Baker[12] diffusion test, which is designed to test the ability of a spermicide to diffuse from a vehicle. In this test, the preparation is smeared about the bottom of a tube, soaked for five minutes with an artificial vaginal fluid and then 1.25 ml semen are "squirted in with a pipette." Certainly the force of "squirting" cannot be held constant, and considerable variation in results must occur. Some mixing therefore occurs, but is undefined in extent. Furthermore, jellies and creams do not "smear" at 37.5°C. as do most suppositories. Consequently, there is no even surface presented to the semen layer, and "pools" of relatively unaffected semen form. In our trials with the method we have experienced considerable difficulties depending upon the nature of the vehicle. Consequently it hardly seems that the diffusion test can be used as a final criterion for efficiency of all types of products. Indeed, the test has been described by Baker himself as yielding less consistent results than other tests.[14]

In using the Sander-Cramer test for the past two years, I have used a new method of mixing which may overcome some objections. Since the method has a final volume of 1.2 ml, there is adequate volume for the introduction of a plastic coated or glass-coated iron lock washer. The tube is then placed in the magnetic field of a synchronous motor, and the washer spun for 5 seconds. Such mixtures have been found to be very homogeneous with no spattering or bubbling. The problem of possible trauma to the sperm appears negligible, since no damage is evident microscopically and since the results fall within the same range as with ordinary mixing. We suspect there may be fewer cases of a single sperm surviving long after immobilization of all others, as is so frequently noted in spermicidal tests.

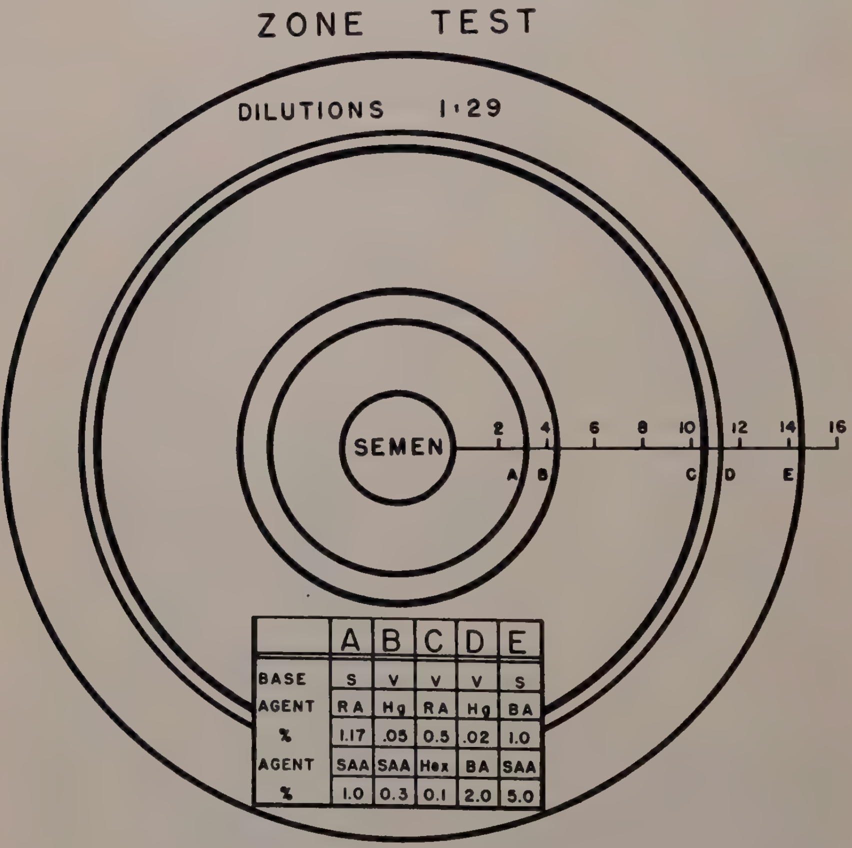
As with dilution, however, mixing and the degree of mixing remains a problem. When mixing is not desired, it has been suggested that the contraceptive and spermicide may be allowed to flow together in a channel, and a note made of the conditions at the interface.[35] However, this is difficult to achieve consistently. With Mr. Arthur Medaugh of our staff we have developed a "zone" test in which artificial mixing plays no part.

The zone test is designed to measure the distance which sperm can migrate into a spermicidal preparation. It is, indeed, a measure of the barrier effect of the vehicle as well as of its spermicidal efficiency. The test is simple to perform: On a microscope slide, a chamber 1 cm² is formed by using shims of thickness 0.025″. In this chamber is spread a layer of the contraceptive under test. The area is covered by a cover-slip containing in its center a carefully-ground 1.5 mm diameter hole. A drop of semen is placed on this aperture and, with an ocular micrometer scale, the distance the sperm travel radially from the central drop is measured. Many preparations may thus be evaluated from the same semen sample. The zone over which the sperms are allowed to migrate is fairly distinct.

The "zone" test is not intended to replace other spermicidal methods, but to give additional information with especial respect to jelly and cream preparations. In a comparative test of preparations of various types, the results shown in FIGURE 5 were obtained. As may be seen in FIGURE 6, the concentrations may be altered by dilution to yield more differentiation between preparations, without altering their relative rank.

Because we were concerned with the fact that temperature may play an important role here, this being a sort of "diffusion" test as well, a variety of preparations were run at 37°C., and are compared with those at room temperatures (FIGURE 7). Studies of this kind are still under way.

Since we have here made mention of "barriers", we may describe a biological contraceptive test which shows considerable promise. Carleton and Florey[22] had tested the effect of various suppositories in the vaginal tract of the dog. In the biological test, as developed primarily by C. G. Hartman, a unit dose of the contraceptive is placed in the vaginal tract of the rabbit. Mating is immediately permitted, and two days later the ova are flushed from the oviducts and examined for cell division. If an interval of five days is employed, the ova may be recovered from the uterine horns. In most cases, the full number of eggs predicted from the number of fresh corpora lutea may be found.



	A	B	C	D	E
BASE	S	V	V	V	S
AGENT	RA	Hg	RA	Hg	BA
%	1.17	.05	0.5	.02	1.0
AGENT	SAA	SAA	Hex	BA	SAA
%	1.0	0.3	0.1	2.0	5.0

FIGURE 5

The conception rate for the untreated rabbit is about 80 per cent in our colony. Most contraceptive jellies and creams tested by us in 1 ml unit doses do not reduce this rate. However, the technic permits us to test pharmaceutical vehicles which may inhibit passage of rabbit sperm into the uterine horns. For example, in one long series of tests no pre-treatment of the rabbit yielded a fertilization rate of 80 per cent. The same rate was observed with a spermicidal jelly in an ordinary vegetable base. When, however, a synthetic-base jelly designed to have "barrier" characteristics but having the same spermicidal value was used, the rate fell to 54.9 per cent. We are not yet certain what factors are involved in rabbit sperm transport across the cervix. Further work is being carried on to analyze the conditions.

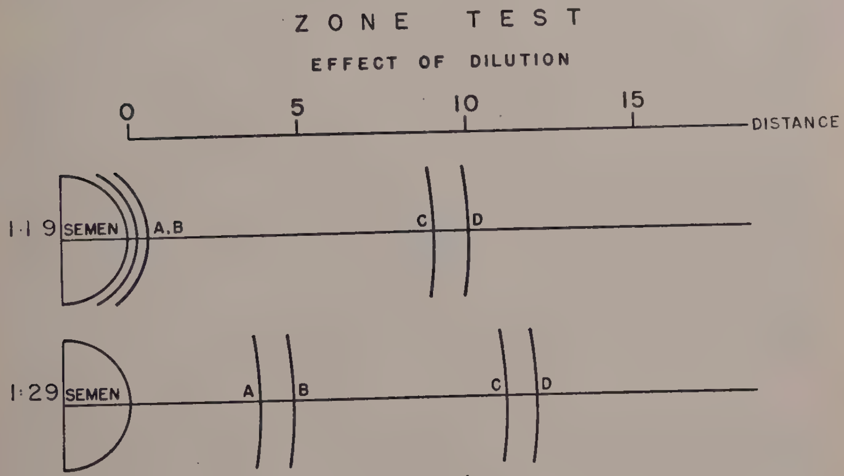


FIGURE 6

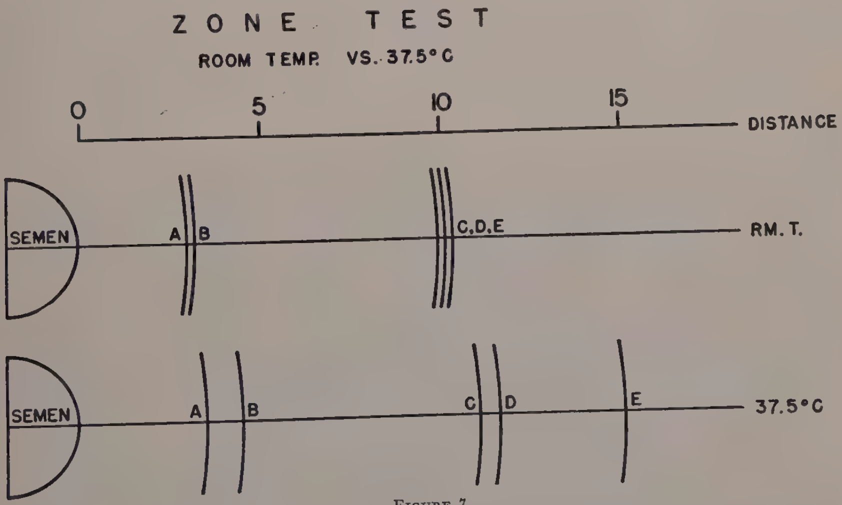


FIGURE 7

Criteria of Spermicidal Activity. It is surprising that, in a field with such a single aim as spermicidal testing, there is so wide a difference in criteria for spermicidal action. Günther[31] was interested in both degree of motility and survivial time; some Baker tests depended upon both of these,[2, 12] while others also involved the determination of least spermicidal quantity[2, 3–6, 12] to kill, in periods from 5–30 minutes.

The Brown-Gamble test[17] determines relative survival times under standard conditions, with a "critical" time of 5 minutes. As described in the New and Non-Official Remedies,[40] the "critical" time is 30 minutes. The Sander-Cramer test[42] is strictly a measure of the least quantity which is spermicidal within 20 seconds, the time needed for the manipulations.

It would appear reasonable to expect, because of its very nature, a good spermicide to be instantaneously effective. Baker, Ranson and Tynen[13] write "there is no branch of pharmacology in which rapidity of action is more important than in chemical contraception." Yet their tests call for 5–30 minutes spermicidal time. Dickinson and Bryant[23] have written that "contraceptive products should be submitted to laboratory tests . . . so that the standard of reliability should not only be maintained but improved upon."

TABLE 5
RELATIVE RESULTS BY VARIOUS METHODS

Prep.	*Method*			
	*B-G** (*N. N. R.*)	*S-C*	*Zone*	*Saturation*
A	1	1	1	1
B	1	1	2	2
C	1	3	3	5
D	1 (2)	4	4	4
E	1	2	5	3

* Performed by independent laboratory.

To improve this standard of reliability, then, is the task of the investigator in this field. In order to achieve this goal, however, he must have some yardsticks with which to measure.

The criterion of instantaneous action at minimal effective concentration in spermicidal tests is considered by us to be the most effective yardstick at present. Such tests are used by us to distinguish (1) between pure spermicidal substances as to potency, and (2) between contraceptive formulations. For this reason, the procedure of rating all preparations which kill within thirty minutes, at dilutions of five-fold, as of equal value (accepted now as a standard test[40]) does not yield enough information.

There is a considerable school of belief that nothing is to be gained by demonstrating the instantaneous spermicidal effect of a highly diluted formula. It avers, in support of this belief, that there is only a given amount of semen, vaginal and cervical fluids with which the spermicide must contend and that this ratio seldom exceeds a dilution of spermicide of about five times by volume. But a medical science cannot rest because an "adequate" preparation has been found. The search always continues to find substances which are more effective; *i.e.*, can be used in smaller amounts, if necessary, with greater efficiency, with less toxicity and less irritation. High dilution ability—a test of minimal effective dose—is a guarantee of spermicidal potency. Furthermore, the practitioner is entitled to an analysis of relative merits. Thus, a method in which the criteria of rapid effect and of minimal effective concentration are lacking tells us nothing about our progress in search of a spermicide, nor anything about the comparative value of one preparation over the other.

We have compared four of the methods discussed here with several commercial preparations. The results are presented in TABLE 5. It is obvious that the preparations are all equal according to the 30-minute standard described in the New and Non-Official Remedies. By the 5-minute criterion of the Brown and Gamble test, only one jelly (actual time 30 minutes) has a rating of second-best. Yet by the Sander-Cramer method, only the first two are of equal potency, while the others assume relative ranks. A further separation is found with the zone and saturation tests, which measure other spermicidal and vehicle properties. It is thus possible to determine whether superior preparations are superior in all properties. It has become standard in our laboratory to test the effect of pure spermicides by the Sander-Cramer test, while the finished preparations are examined not only by that test and the Brown-Gamble test, but also by "saturation" and "zone" tests.

In reviewing the state of the science at the present date, a sincere tribute is offered those pioneers, who, like Dr. Gamble, gave much in time and labor to develop practical tests. It is certain that not all the problems discussed here have been overcome, although it is hoped that the suggested new tests will solve some of them. Details of their performance and results will appear in future publications. We confidently expect that the next decade will provide major developments in spermicidal testing.

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Discussion of Paper by Doctor Millman

Doctor Clarence J. Gamble (*Milton, Mass.*): The clinical tests of the effectiveness of contraceptive materials are difficult to arrange. Each failure costs much in goodwill to those directing the test, and in expenses of delivery and upbringing to those participating. The results, too, are extremely inaccurate because of unreported failures to use the prescribed contraceptive. For this reason, laboratory tests have been sought on which estimates of presumed contraceptive effectiveness may be based. Most of these have measured the power of the contraceptive material to immobilize spermatozoa.

In describing one of these tests, Brown and Gamble[1, 2] pointed out that the complete mixing of semen and the diluted contraceptive material (which is necessary to secure a known concentration in all parts of the observed sample) has no counterpart in clinical contraception.

Another variation from clinical conditions arose from the fact that, to allow time to observe the instant of immobilization after complete mixing, the jelly was diluted with a 0.9 per cent solution of NaCl. They chose four parts of diluent to one of contraceptive to provide conveniently measurable immobilization times. Since the volume of the usual ejaculate is approximately equal to the usual dose of jelly or cream they used equal parts of semen and diluted contraceptive, employing arbitrary proportions of contraceptive, saline solution, and semen of 1:4:5, respectively. As they stated, dilution to this extent is not present in the postcoital vagina.

Employing these proportions, it was found that all discoverable spermatozoa were immobilized within five minutes by many of the commercial contraceptive mixtures. Since the proportions employed would require, with the usual 5 cc. dose of contraceptive material, an ejaculate of 25 cc. to reproduce them in the postcoital vagina, a quantity far beyond the usual, the authors did not consider higher dilutions of any value in estimating clinical effectiveness.

The saturation test described by Millman has the advantage that the dilution is entirely by semen, reproducing clinical conditions in this respect.* It permits comparisons of immobilizing power after high dilutions, dilutions well beyond that of the Brown and Gamble method. This is made possible, only by the use of relatively large quantities of semen and requires the time of the operator necessary for successive additions and observations.

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* The importance of approximating clinical conditions by using human semen is shown by the finding that it may give results different from those of other spermatozoal suspensions. Spermicidal times of a series of commercial contraceptives were determined by the Brown and Gamble method and by a modification of the method in which a laboratory, unable to secure human semen, used an intelligently chosen sample of guinea pig sperm suspended in an egg-white medium.

The results were approximately the same for many of the mixtures. Those whose activity was found to be markedly less when tested with semen appeared, from their formula, to act chiefly through their acidity, suggesting that the buffering power of the semen may have caused the differences. The materials which showed lower activity with the guinea-pig-egg-white mixture contained mercurial compounds which may have been inactivated by the egg white.

Since the usual dose of contraceptive is approximately equal to the semen, differences in immobilizing power at the high dilutions may not be associated with differences in clinical effectiveness.

The saturation test, as does that of Brown and Gamble, requires complete mixing, a procedure which does not occur after ejaculation in normal intercourse.

The diffusion test of Baker, Ranson and Tynen,[3] described by Millman, is an intelligent attempt to approximate clinical contraception by the avoidance of complete mixing. In removing a sample from the semen, however, after it has overlain the contraceptive material in the test tube, there is no certainty that the portion taken is representative of all levels. There is no way of knowing whether it comes from the top, middle or bottom layer of the semen, each, presumably, undergoing a different reaction to the immobilizing agent. Furthermore, the process of taking successive samples, as prescribed, will stir the semen to an extent possibly greater than that in the postcoital vagina.

Millman's zone test of immobilizing power is an ingenious method of avoiding the unclinical procedure of mixing. Since the distance of penetration of the spermatozoa into the diluted contraceptive mixture may be presumed to be in direct relation to their survival time, the method appears to have elements common to other measures of spermicidal time. It differs from many previous methods in that the non-spermatozoal elements of semen are presumably left behind, since the progress of the naked sperm is probably much faster than that of molecular diffusion.

The high dilutions used and the short distances traversed suggest that the penetration of sperm into undiluted jelly is minimal, and that the clinical immobilation occurs chiefly in the semen. In this respect, therefore, the zone test differs from clinical contraception. The high dilutions used have the disadvantages already mentioned.

The author's use of animals to determine contraceptive effectiveness is a well-reasoned step in bridging the gap between laboratory immobilizations and the final clinical test, which should be made with the anatomy and the secretions present in the human vagina.

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A METHOD OF CONTRACEPTION WITHOUT DIAPHRAGM—A TWO-YEAR INVESTIGATION

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This study was undertaken because of the desire to find a simpler, more efficient means of planning parenthood. In this enlightened era, the need for family limitation is so well established that it is not necessary to elaborate extensively on the reasons for it. The Whelpton and Kiser[1] study shows that 90 per cent of the couples under investigation tried to control pregnancy. The role of contraception in preventive medicine is widely accepted. Toland[2] speaks of "preventive medicine as the promotion of health and happiness of individuals, rather than—an avoidance of something noxious."

Weiss and English,[3] in considering anxiety and contraception, state "There can no longer be any question regarding the necessity for planned parenthood. This makes it important that a satisfactory contraceptive method be made available and this in turn will give married people freedom from what may be termed normal anxiety in their sexual relations. It is true that some people have scruples against the use of contraceptives, but these scruples seem to be diminishing each year as the importance of human health and happiness are given a more prominent place in our thinking."

Many married couples engage in sexual union with the thought that their indulgence will not result in pregnancy. Regardless of religious belief, every parent wishes to control the number of offspring, and much difference of opinion prevails regarding the mechanics of implementing this wish. The marked improvement in maternal and infant mortality and morbidity statistics[4] in the last twenty years is due to the widespread availability of contraceptive information as well as to the improved methods of treating these patients. A large number of the bad risks are screened out by conscientious physicians who prescribe contraceptive advice to them.

In evaluating a method the following points are considered: (1) effect on the tissues, absence of irritation; (2) ease of administration (simplicity is paramount; mechanical occlusive devices may be difficult to insert and not widely applicable.); (3) suitability of the method from an esthetic standpoint (it must be non-odorous and non-staining.); (4) ease of dispersion (the material should spread readily over the vaginal mucosa and into the rugae, rapidly mix with vaginal and seminal fluids and secretions, adhere tenaciously to moist surfaces, and form a dense barrier over the external os of the cervix.); (5) rapidity of spermicidal action (the agent should be easily miscible with the semen to ensure complete spermicidal action.); (6) proven fertility of the group under study.

The studies of Baker, Ransom and Tynen[5] suggest that the ideal contraceptive should also be inexpensive, unaffected by the ordinary range of climate and easily portable. Stein and Cohen[6] feel "that it must prove acceptable to both husband and wife; it must always be within easy reach; it should not lessen natural desires and responses . . . ."

Material and Method of Study. Preceptin,* the material chosen for study, is a smooth, white, odorless gel containing ricinoleic acid and p-diisobutylphenoxy-polyethoxyethanol in a synthetic base, buffered at pH 4.50.

Our investigation is concerned principally with evaluating these factors: (1) Effect on tissues; biopsies of the vaginal mucosa were taken on subjects who had not used the gel and on subjects who had used it for 6 weeks, 9 months and 16 months respectively (Figures 1–4). (2) Dispersibility. X-rays and colored photographs were taken to demonstrate this (Plate I, Figures 5, 6 & 7); they were taken before and after the introduction of the preparation into the vagina and again at varying periods following coitus. Five and ten per cent Lipiodol Lafay was added to the gel for the X-ray studies. Five-tenths per cent gentian violet was added to the preparation for a few of the colored pictures and 0.5 per cent charcoal for some others but the majority of the photographs were taken with the plain gel. (3) Effectiveness in preventing conception. (4) Esthetic acceptability. (5) Proven fertility of the group under study.

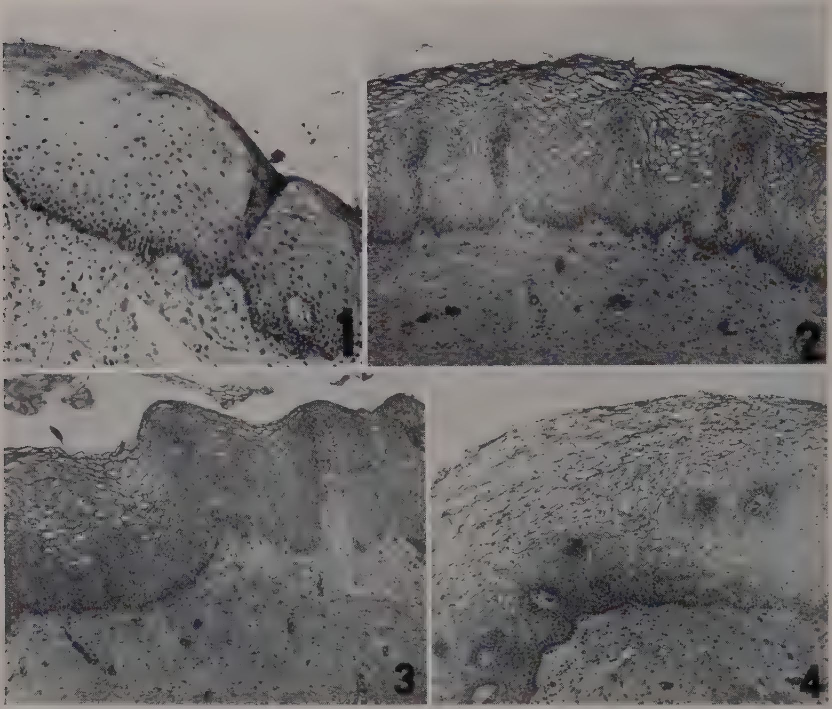

Figure 1. Control biopsy of vaginal mucosa. Figure 2. Biopsy of vagina after 6 weeks of gel. Figure 3. Biopsy of vagina after 9 months of gel. Figure 4. Biopsy of vagina after 16 months of gel.

The three latter factors were evaluated by analysis of the returns from a questionnaire and a study of 704 histories. The project was begun in August,

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* Preceptin vaginal gel, formulated and supplied by the Ortho Research Foundation, Raritan, New Jersey.

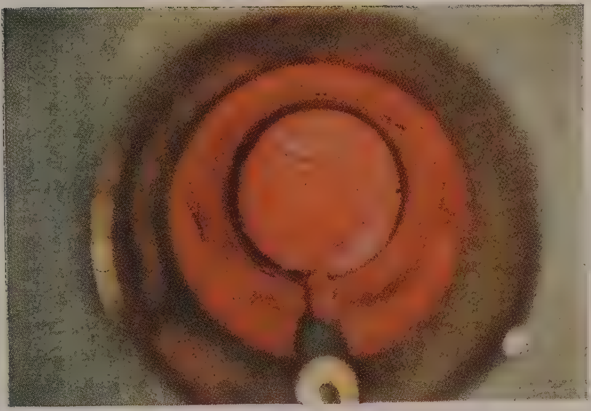

FIGURE 5.
Cervix before insertion of Preceptin gel.

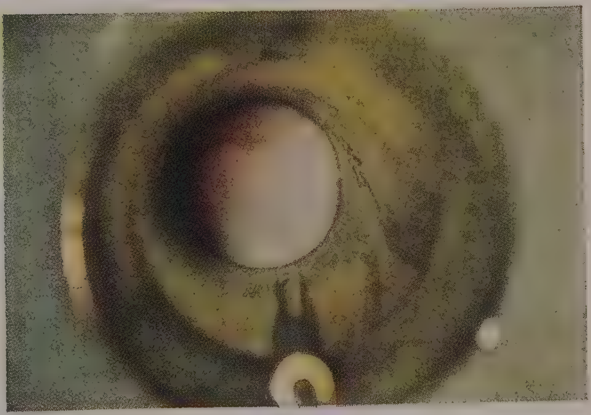

FIGURE 6.
Cervix 5 minutes after insertion of preceptin gel.

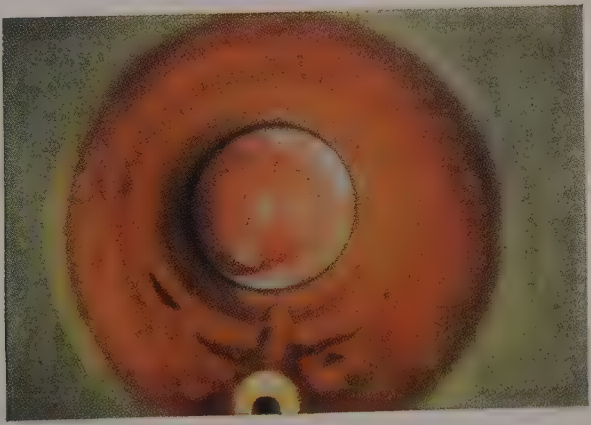

FIGURE 7.
Note coverage of cervix. Same cervix 8 hours after coitus. Note occlusion of cervical os by the gel.

1949. The subjects are all private patients. They were selected from among individuals who: (1) requested contraceptive advice at premarital or postpartum examination; (2) were referred for this information because of medical indications; (3) had a contraindication to an immediate pregnancy.

The preparation being evaluated was not used on all patients handled during this period, since a number, for various reasons, expressed a desire for other methods such as diaphragms, condoms or basal temperature readings.

A small group of patients about to undergo hysterectomy were given the gel with dyes added. The material was placed in the vagina to demonstrate its spread over and into the cervix. This phase of the investigation is not completed but will be reported when sufficient data are available to draw conclusions. At the present time we are satisfied to state that we are very much impressed by the dispersion qualities of this preparation.

The gel is contained in a collapsible tube, and a transparent non-breakable applicator which threads onto the tube is provided for measuring the proper dosage. There is no need to guess regarding the correct amount. Patients are instructed to insert one applicatorful in the vagina prior to each coitus. Douching is unnecessary. It can be stated that the gel aids materially in maintaining normal physiological conditions in the vagina.

At the end of this present study in August 1951, the gel had been given to 704 patients. In order to accurately evaluate tolerability, effectiveness and esthetic acceptability, the following questionnaire was given to about 400 of these subjects and our conclusions on these points are based on an analysis of 203 completed questionnaires.

Questionnaire

Name________________Address________________Date________

1. How long have you been using Preceptin?
2. How many pregnancies have you had previous to using Preceptin? Were these pregnancies planned?
3. What other types of contraceptives did you use previously?
4. Do you prefer Preceptin? Why?
5. Are you satisfied with this method of planned parenthood? Why? Your husband's opinion.________________
6. Do you find Preceptin too difficult to use? Why?
7. Do you find Preceptin too inconvenient to use? Why?
8. Are there any signs of irritation to you? Explain.
9. Are there any signs of irritation to your husband? Explain.
10. Other remarks:________________

Analysis of these questionnaires reveals the following data: 168 were previously pregnant; 29 were not; and six did not specify.

The total number of previous pregnancies in the above-mentioned 168 patients was 311. The number of patients who had previous planned pregnancies was 66.

Ninety persons had not used any type of contraception previously; 85

had used a diaphragm; 15 had used a condom; seven had used the rhythm method; three had used jelly alone; two had used suppositories; and one had used douches.

Of pregnancies following the use of the gel, five were planned; 11 were due to irregular use; five ran out of the preparation; and 13 had used the preparation regularly.

One hundred and forty-eight persons preferred the gel to all other types of contraception, 24 did not, and 31 were undecided.

One hundred and eighty three patients reported 1098 months of effective contraception with the preparation under study, an average of six months per patient.

In religion, 83 per cent were Protestant; 16 per cent were Catholic; and one per cent were Jewish.

Reasons and comments expressed after using the new preparation varied from "Best method ever used," to "It failed."

Considering the failures, one must admit that no method gives 100 per cent protection. This study indicates that this preparation is more effective than any other method we know.

The comments of the husbands were entirely favorable and enthusiastic. The naturalness of the method and absence of a device detracting from the normal sensation were repeatedly observed.

Patients with planned pregnancies become pregnant within one, or no longer than two months, after discontinuing the use of the gel. Of two patients who claimed regular use and reported failures, one stated it was the end of the container and the other that the container was cracked. There may have been some dehydration and diminution in dispersibility of the agent in these cases. Another reported failure after having coitus in the evening and again in the morning without using another applicatorful of the preparation. We gave the gel to a total of 704 patients. The number of failures in this group, a total of 13, is based on a careful study of the 704 charts to determine whether or not pregnancy had occurred in these patients.

The enthusiasm with which this new method of contraception is received has convinced us that it is esthetically acceptable. The points: simplicity, ease of administration, convenience and satisfaction were expressed so emphatically and repeatedly by users that we are inclined to accept these judgments. Seventy-two and nine-tenths per cent favored the new preparation. Eleven and eight-tenths per cent were not satisfied and 15.3 per cent were undecided. One hundred thirteen patients or 55.6 per cent had used some other method of contraception. The study was conducted on a predominant number of women with proven fertility. One hundred sixty-eight, or 82.7 per cent, had had one or more previous pregnancies. The space of two years necessarily places some limitation on our period of evaluation. Some of the questionnaires were completed as long as eight months ago and patients are continuing to use the gel with success. Only two instances of sensitivity have been reported.

The studies of Rakoff and Casper[7] have shown that water-dispersible jellies are among the most satisfactory means of introducing medications into the vaginal tract. They can be buffered to prevent alteration by the secretions and yet be retained in the vaginal tract for many hours. These investigators have shown that the jelly can be easily introduced and have made X-ray studies demonstrating the dispersion qualities. These agents mix readily with the vaginal secretions and our post-coital studies show that it mixes easily with semen in the vagina.

Several previous studies[8–12] have been made on jelly-alone techniques for contraception. It was the conclusion of these studies that this is an effective method. It is our feeling that no jelly previously studied has the dispersible and semen miscible qualities of Preceptin vaginal gel.

Summary. 1. A critical evaluation of a new contraceptive agent has been made as to its effectiveness, esthetic acceptability, dispersible qualities and effect on tissues.

2. X rays and colored photographs were taken to demonstrate that this gel spreads readily over the vaginal mucosa and into the rugae, rapidly mixes with vaginal and seminal fluids and secretions, adheres tenaciously to moist surfaces, and forms a dense barrier over the external os of the cervix.

3. All biopsy specimens, whether at six weeks, nine months, or sixteen months after the use of the gel, show perfectly normal human vaginal mucosa. They are taken from women with normal endocrines, as indicated by the thickness of the squamous epithelial layer and the presence of glycogen. If there were the slightest irritation, sub-mucosal round-cell infiltration and an accumulation of leucocytes would result. These are conspicuous by their absence. It would be difficult to find more nearly normal human vaginal biopsies.

4. Over a period of two years, 704 patients were given this new gel. Questionnaires were given to 400 of these patients and answers from 203 are tabulated.

5. One hundred forty-eight patients (72.9 per cent) have expressed a preference for this method of contraception. Thirty-one are undecided, and 24 or 11.8 per cent do not care for the method.

6. A predominant number were of proven fertility—168 or 82.7 per cent.

7. During the two-year study of this contraceptive gel, conception was not effectively controlled in only 1.8 per cent of the 704 patients who claimed regular use.

Conclusion. This contraceptive preparation is not harmful to the tissues, has excellent dispersion qualities, is effective and esthetically acceptable to a number of critical patients.

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CLINICAL EXPERIENCE WITH A NEW GEL-ALONE METHOD OF CONTRACEPTION[*]

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The ideal aim in a contraception program is to furnish patients with a method which is highly effective and, at the same time, simple to use. The ingredients of the contraceptive must be non-irritating, non-toxic, and should have no other unpleasant features. In spite of the widespread recommendation of the standard combination of diaphragm and jelly, this method falls far short of such aims. The bother to prepare and insert the diaphragm and, at times, the mechanical interference with intercourse are valid criticisms and account, in part, for the lack of routine use of the occlusive diaphragm and jelly. It is well known that failures result from this technique and the explanation lies both in the method itself and in careless use. In recent years, attempts have been made to overcome this objection of complicated technique through the use of standard contraceptive jellies alone and through the use of the contraceptive suppositories. A higher degree of acceptability, and longer continuous use, therefore, has unquestionably resulted. According to separate reports of Stein, Garvin, and Eastman, it appears that the effectiveness of these simpler means is substantially the same as that of the diaphragm combined with jelly or crème.

Having shown that simplification of method, without changing the composition of the contraceptive ingredient, does not increase the risk, it naturally follows that an effort should be made to try to find a contraceptive formula with potentially greater effectiveness. Accordingly, in November 1949, we began a clinical study of an improved contraceptive preparation to be used alone.

This preparation[†] contains p-diisobutylphenoxypolyethoxyethanol and ricinoleic acid as active ingredients. As mentioned in the earlier paper by Dr. Hunter, it is a gel buffered to pH 4.5. It has a rapid spreading action, yet adheres satisfactorily to moist mucosal surfaces and readily mixes with seminal secretion. It is stable, non-greasy, odorless and white. It is of practical importance, especially for a jelly-alone method, that spermicidal time is only 20 seconds with its use, even when the gel is diluted 50 times. The gel is several times more spermicidal than other jellies. Unlike contraceptive suppositories, which require four to ten minutes to liquify at body temperature, no waiting period is needed. Prior animal experiments at the Ortho Research Foundation have shown that the gel does not cause mucosal irritation and that absorption from vaginal surfaces is negligible. No heavy metallic ion is involved.

Study Program. Opportunity for study of this new gel, Preceptin, as sole means of birth control was afforded by patient volunteers from our group private practice and by women attending the Hennepin County (Minneapolis) League of Planned Parenthood. The gel was offered as an optional method and was selected as such, or patients asked specifically for it having heard of it from others attending the office or clinic. It should be emphasized that, in both locations, the standard contraceptive technique recommended, was (and still is, by other associates) the diaphragm-jelly combination. Patients attending the clinic are largely from a low-income class, a few of whom are negroes. The study was inaugurated on December 1, 1949, but for purposes of analysis, patients receiving the gel after August 15, 1951, have not been included, since the remaining trial period is deemed too short for evaluation.

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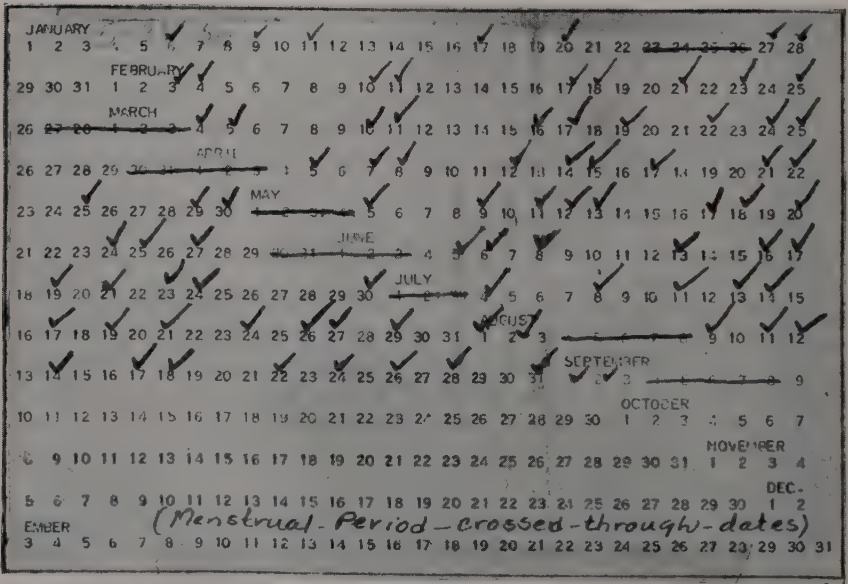
[*] Appreciation is expressed to Dr. Katherine Kuder, for her help in the study and critical review of this paper. We wish also to thank Dr. Claude Ehrenberg, Medical Director, Hennepin County League of Planned Parenthood, for his permission to conduct the clinical study.

[†] Preceptin vaginal gel, formulated and furnished by the Ortho Research Foundation, Raritan, New Jersey.

Instruction in the use of the applicator and gel by individual demonstration was given to each patient. While the use of the contraceptive gel can be easily taught by nurses or medical students, it was felt that the results would be more reliable if we were solely responsible. Advice to the patient was as follows: (1.) Introduce full applicator of Preceptin deeply into the vagina. Press in the plunger and then remove the applicator (without drawing back on the plunger.) The gel may be introduced up to one hour before intercourse. If desired, intercourse may immediately follow the introduction of the gel. If intercourse is repeated, an additional applicatorfull is necessary. (2.) Do not douche for eight hours. Douching is optional thereafter. (3.) Do not use the gel with any other contraceptive, such as a diaphragm or condom. (4.) Keep a record of menses and times of coitus.

Each patient was supplied with a menstrual-record calendar printed for one year on a 4″ x 6″ card. She was advised to mark "X" on each date of


JANUARY
FEBRUARY
MARCH
APRIL
MAY
JUNE
JULY
AUGUST
SEPTEMBER
OCTOBER
NOVEMBER
DEC.
EMBER

(Menstrual-Period-crossed-through-dates)

FIGURE 1.

coitus and to line out the days of menstruation, as shown in the sample card.

Clinic patients were interviewed in a routine manner after one week, and each time when they returned for more of the gel. In the cases of those patients who failed to return, follow-up contact was attempted in six months.

Private patients were asked to return in one week, but, for the most part, opportunity for interview came only when they returned for additional supplies. All interviews were personally conducted by us.

A final direct survey was made of all patients, both clinic and private, save those previously deleted from the study. Women thus excluded were those who: (a) did not use the gel regularly; (b) could not be contacted; (c) voluntarily discontinued its use for one of the following reasons: lack of confidence, messiness, irritation, religious reasons, and indifference. It is interesting to note that, in many instances, the lack of confidence was expressed by other physicians and by the husband, rather than by the patient herself. An occasional complaint, earlier in the study, was irritation. This, however, was largely eliminated by a slight modification in the buffer system of the gel. The final survey was made by personal interview, telephone interrogation, or letter contact. Such inquiry was made by us or by a professional assistant during the last two weeks of September. Four hundred and ninety-eight women were thus contacted and this number serves as the basis for our report.

TABLE 1
PATIENT DISTRIBUTION

	Clinic	*Private*	*Total*
Group A	246	221	467
Group B	179	129	308
Group C	115	116	231

Results. A total of 634 patients (348 clinic and 286 private) were given Preceptin during the survey period. Of this number, 266 clinic and 232 private patients, totalling 498, were recently interviewed after 136 patients were eliminated for reasons already mentioned. An additional 31 women were excluded from the study by the final interview, again largely through false lack of confidence and scant use. To anticipate criticism on this point, we wish to emphasize the fact that, to our knowledge, no pregnancies occurred during the brief use of the gel in any of the 167 patients so eliminated.

Two hundred and forty-six clinic and 221 private patients, a total of 467 women, used Preceptin for two or more months (group "A"). If only those women who used this gel 6 months or more are included, which we shall term group "B", the number is reduced to 179 clinic, plus 129 private patients, a total of 308. Two hundred and thirty-one patients returned calendar cards to us in the past four weeks. Of these, 115 were from clinic members and 116 from our private practice (see TABLE 1, Group C).

For purposes of determining pregnancy rate, and effectiveness of the contraceptive, the conventional method is to base statistics on woman-months of exposure. Summation of our data is given in TABLE 2. A total of 14 true failures are recorded; but this, however, can be corrected to five failures if patients are excluded who used the gel less than six months.

Pregnancy rate is determined by multiplying by 1200 the number of failures divided by the number of woman-months exposure. The effectiveness of the contraceptive is calculated by the following formula, "X" being the expected non-contraceptive pregnancy rate.

$$\text{E}\ (\%) = 100 - \left(100\text{X}\ \frac{\text{Pregnancy rate}}{\text{“X”}}\right)$$

For practical purposes it was impossible, in our study, to determine the non-contraceptive rate before use of the gel, since many patients had previously used other types of contraceptives. In lieu of a control standard from the Minneapolis series, we have accepted Cavanaugh's recently published figure of 80. He derives this from the Sloan Hospital experience, plus a compilation of eight other investigations. We have calculated both pregnancy-rate and effectiveness for each of the groups. They are recorded in TABLE 3. It will be noted that pregnancy-rate for our entire group was just over four. As will be shown later, this is considerably better than other reports in the literature including other jelly-alone methods. If short term users are eliminated, a corrected figure of 1.7 pregnancies with an effectiveness of nearly 98 per cent is calculated. Analysis of those reporting who have kept detailed calendar records gives substantially the same gratifying statistics.

TABLE 2
WOMAN-MONTHS EXPOSURE AND FAILURES

	Clinic	*Private*	*Total*
Group A	2272 (8)	1774 (6)	4046 (14)
Group B	2029 (2)	1470 (3)	3499 (5)
Group C	1197 (2)	1078 (2)	2275 (4)

While the above data record our experience from a scientific point of view and one which is suitable for comparison with other reports in the literature, it is our belief, as already expressed by Dr. Hunter, that the number of patient failures, compared with the number of patients who received the contraceptive, is of more practical concern. In this regard, our 14 failures in 467 women using Preceptin two or more months, gives a rate of 2.99 per cent. The same method of calculation based on the corrected number of 308 women, those who used it six months or longer, gives a failure rate of only 1.62 per cent.

It is of interest to note that, during the 22 month study period, 19 patients

(14 private and five clinic) voluntarily discontinued the use of the contraceptive jelly in order to become pregnant. Sixteen of these 19 women became pregnant within six months and 14 conceived within one month!

Discussion. Any new contraceptive which purports to be superior to those already available must possess: (1) increased reliability; (2) simplification of use; (3) improved acceptability; or a combination of all three attributes.

The standard practice of birth control clinics in measuring the chance of conception is to calculate pregnancy rate per 100 woman-years of exposure.

TABLE 3
PREGNANCY RATE—EFFECTIVENESS BY PER CENT*

	Clinic		*Private*		*Total*	
	Rate	*Per cent*	*Rate*	*Per cent*	*Rate*	*Per cent*
Group A	4.2	94.8	4.0	95.0	4.1	94.9
Group B	1.1	98.6	2.5	96.9	1.7	97.9
Group C	2.0	97.5	2.2	97.3	2.1	97.4

* Based on estimated non-contraceptive pregnancy rate of 80.

TABLE 4
RELATIVE EFFECTIVENESS OF CONTRACEPTIVE TECHNIQUES

	Months of exposure	*Number of failures*	*Pregnancy rate*
Diaphragm—jelly:			
New York	18,012	185	12
New York (Sloan)	2,472	34	16
Nashville	5,542	81	18
Philadelphia	13,305	163	15
Suppository:			
Baltimore	4,210	39	18
Jelly—alone:			
Chicago	2,892	47	20
Philadelphia	720	9	15
The new gel alone:			
Minneapolis	4,046	14	4

This is the practice we have chosen in order to compare results with other methods. TABLE 4 has been constructed from reports on diaphragm-jelly combination, standard jelly-alone, and suppository methods. Our figures are included.

It is apparent from a review of these figures that the new gel used alone is outstandingly superior to the other methods compared.

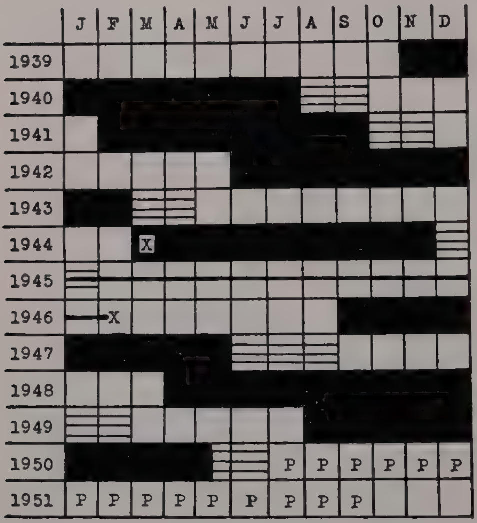
While a statistical expression clearly indicates the reliability of this gel, the following three case reports show even more clearly the protectiveness of this contraceptive.

Comments from these women were, "I couldn't be fitted with a diaphragm; have found Preceptin completely dependable", and "At first I thought nothing would help me and now I have a lot of faith in it", and "it's wonderful, certainly better than a diaphragm." The comments are typical of the views of both clinic and private patients.

Dependability of Preceptin is further evidenced by the regular users who formerly relied on other contraceptives which failed. A total of 98 previous true contraceptive failures were recorded: 54 with the occlusive diaphragm and jelly, 22 condom, 10 jelly-alone, and 5 suppositories. Several patients gave a history of more than one failure using a diaphragm all of the time.

Added proof of the reliability of the new gel, as well as fertility of the women under study, is given by our small series of patients who discontinued using it to become pregnant. As previously mentioned, 14 of the 19 patients immediately conceived.

CASE REPORT OF PATIENT Mrs. D.D.



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Married 10/31/39.
Del. 7/29/40. 2 mo. amenorrhea.
Del. 9/30/41. 2 mo.      "     .
Del. 2/28/43. 2 mo.      "     .
Del.11/30/44. 2 mo.      "     .
   Husband in Army from
   Mar. 1944 to Jan. 1946.
Del. 5/21/47. 3 mo. amenorrhea.
Del. 1/3/49.  2 mo.      "     .
Del. 5/15/50. 2 mo.      "     .

Previous contraception:-
   interrupted coitus and
   rhythm throughout.

Preceptin given July 1950.

            - - -

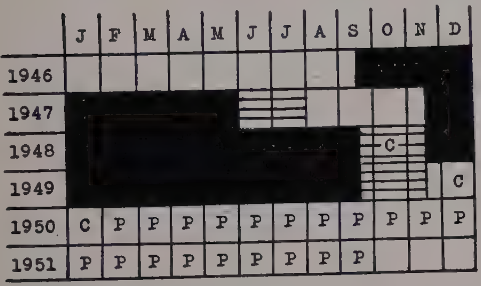
7 pregnancies in 10 years.
Husband in Army 2 years X---X.
Preceptin protection (P) for
   the past 15 months.
```

FIGURE 2.

Acceptability and the simplicity of use of Preceptin are, without doubt, salient features. In spite of the reluctance of women, particularly private patients, to accept and use a new contraceptive product, women given the option of the standard diaphragm-jelly combination, or a simple but experimental method of gel alone (and this was so stated), have chosen the latter in nearly 50 per cent of the cases. This was true not only for women with previous contraceptive experience (234 cases), but for patients requesting contraception for the first time as well. Again, it is strikingly significant that, in less than 24 months from both private and clinic offices where for years the diaphragm-jelly combination was prescribed (and where that same method is currently being recommended by other doctors) 634 women selected, on a preferential basis, an experimental gel-alone method. This can be explained only by virtue of the relative simplicity of its use and/or dissatisfaction with other methods.

The convenient method of use of Preceptin recommends it to the doctor or nurse instructor as much as it does to the patient. We have found the applicator administration of the gel considerably easier to demonstrate to patients than the use and introduction of the diaphragm and jelly. The time involved is practically one-fifth of that required for the diaphragm technique. While the ease of use may be said to favor selection of Preceptin contraception, we have not been altogether surprised to learn that many patients discontinued its use, fearing that such a simple device must, of necessity, be risky. A few such skeptics have since returned to routine use of the preparation.

CASE REPORT OF PATIENT Mrs. G.T.

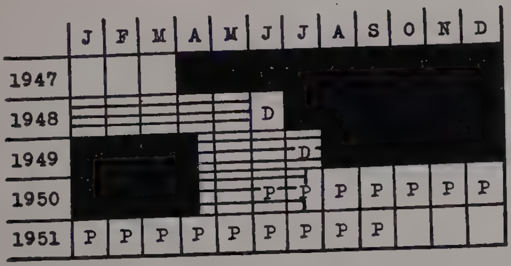


Married 6/14/45.
L.M.P. 9/13/46.
Delivered 6/4/47.
2 months amenorrhea.
No contraceptive thereafter.
L.M.P. 11/22/47.
Delivered 9/12/48.
2 months amenorrhea.
L.M.P. 11/23/48.
Condom failure.
Delivered 9/19/49
2 months amenorrhea.
Condom used until
Preceptin given Feb. 1950.

Three pregnancies in 3 years.
One Condom (C) failure.
Preceptin (P) protection past 20 months.

FIGURE 3.

CASE REPORT OF PATIENT Mrs. A.S.



Married June 1946.
L.M.P. March 1947.
Delivered 1/6/48.
5 months amenorrhea.
L.M.P. July 1948.
Diaphragm failure.
Delivered 4/11/49.
3 months amenorrhea.
L.M.P. 8/1/49.
Diaphragm failure.
Delivered 4/12/50 (Twins).
3 months amenorrhea.
Preceptin given June 1950.

3 pregnancies; 4 children in 4 years.
Two diaphragm-jelly (D) failures.
Preceptin (P) protection past 15 months.

FIGURE 4.

It must follow automatically that, with the ease of use and the immediate effectiveness of the gel, there will be a considerably greater number of women using this method exclusively. While we have no data to bear out this contention, the logic of the view would seem to render it acceptable. Certainly, if contraception is to be employed, the aim is to prevent pregnancies as completely as possible, and over as long a period of time as is desired. Any method which favors routine, rather than haphazard, use is

CALENDAR CHART OF PATIENT MRS. M.H.
DAY OF CYCLE

Date onset menses	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
1/23	//	//	//	///	X	X						X	X						X	X						X	X			X		X			X
2/27	//	//	//	///	///	X	X					X	X					X	X		X			X		X	X								
3/30	//	//	//	///	///		X		X	X				X		X	X		X				X	X			X				X	X			
5/1	//	//	//	///	X				X		X	X	X				X	X		X				X	X		X								
5/30	//	//	//	///	///		X	X		X					X			X	X		X		X		X	X						X			
7/1	//	//	//	X				X			X		X	X			X		X		X			X		X	X		X			X	X		
8/4	//	//	//	///	///	X		X	X		X			X	X				X		X		X		X			X	X	X					
9/4	//	//	//	///	///																														

X—Coitus ///—Menses.

FIGURE 5.

at once more valuable, and this is decidedly the case in the use of Preceptin. Although certain minor objections are occasionally raised, such as messiness and irritation, the overall acceptability of the product is an outstanding feature.

Discussion of this report is not complete without further mention of the 231 cards returned to us, recording menstrual times and dates of coitus. Analysis of these records reveals only one woman who consistently avoided intercourse at her fertile period. At the same time, there were four others who thought they were doing so, but actually were planning coitus (with Preceptin) at the most fertile time. None of these and only four in the entire series became pregnant while using Preceptin regularly. Another interesting observation was the finding that only 31, or 13 per cent of these patients had consistently regular periods. It would appear, therefore, in this series at least, that rhythm, as a means of contraception, is highly risky. The following chart (FIGURE 5) has been prepared from the original calendar card kept by a patient and previously shown, as an example of the records kept by the 231 patients in this study. This patient always used Preceptin and her chart shows that coitus took place at any time during the cycle, including many exposures during the fertile period, yet conception did not occur. The irregularity of her menstrual cycle can also be observed.

Summary. A study was undertaken of 634 women who used a new type contraceptive gel-alone having improved spermicidal characteristics. Careful follow-up was made of the entire series. In all, 14 failures occurred in 4,046 woman-months exposure, giving a pregnancy rate of 4. This figure is substantially less than pregnancy rates reported from other series using jelly-alone, suppositories, and disphragm-jelly combinations. Additional evidence of reliability of Preceptin was given in case reports, by statistics on previous contraceptive failures, and by ease of conception after voluntarily discontinuing the preparation.

Acceptability of the method is attested by the sizable number of users selecting it in preference to available standard diaphragm-jelly methods. It is easy to instruct the patient in the use of Preceptin, and because of this simplicity of use, more regularity and better results can be expected.

Two hundred and thirty-one conscientious patients kept card records of dates of menses and coitus. Analysis of these cards revealed no hesitancy by the patient in having intercourse at any time of the month, including the so-called "fertile period". Only 13 per cent of the cards showed a regular menstrual pattern.

Conclusions: (1) Preceptin was given to 634 private and clinic patients. Of this number, 467 patients had used the gel for 2 to 22 months, giving a total of 4046 woman-months exposure. (2) Expressed in terms of failures per woman-months of exposure, the pregnancy rate in this study was 4.1 for the entire group. (3) There were five pregnancies in the series of women using Preceptin six months or more, an effectiveness of 97.9 per cent.

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Discussion of Paper by Doctors Stromme and Rothnem

Doctor Alan F. Guttmacher, *Sinai Hospital and The Johns Hopkins University School of Medicine, Baltimore, Maryland.* At Sinai Hospital, we have a research clinic in contraception under the direction of Dr. Ruth Finkelstein and have had limited experience with Preceptin. We have prescribed it to 136 patients for a period of one month in the shortest case and fourteen months in the longest case. Thirteen patients discontinued its use for various reasons.

There have been two unplanned pregnancies among the 123 users. One occurred after one month of use and the other after three months of use. We have not tallied the years of exposure which this series represents but we would estimate it to be 70–75 years. If this is true, our experience would show a pregnancy rate of approximately three per one hundred years.

Discussion of Papers by Doctors Hunter, Darner, Gillam, Stromme, and Rothnem

Doctor Clarence J. Gamble, *Milton, Mass.:* Any physician who attempts to estimate the effectiveness of a contraceptive method deserves sympathy, for he must depend on the user to tell him whether it has been employed correctly and on every occasion of need. An unpleasant oral medicine can be dissolved in sufficient water to allow the physician to see it swallowed, but such observation is obviously impossible with contraception. As all methods, except sterilization, have their unacceptable features, omissions are apt to occur and sexual taboos and feelings of personal pride often make their reporting incomplete.

In a clinical study of contraceptive suppositories, for example, now being made in Maryland, the user is asked at each visit if they have been employed on every occasion. Those who have repeatedly claimed complete regularity will often give a different report for the same period of time after pregnancy has become obvious.

Unduly high estimates of effectiveness have sometimes been made by the observers who intensively question each patient who becomes pregnant and omit her from their computation if one or more omissions are admitted.

There can be no assurance in such cases that the conception occurred at the time of the omission.

The accuracy of the results might be somewhat improved if every patient were catechized with equal severity even if not pregnant, and taken out of the series if an omission is admitted. It seems probable, however, that even with such a procedure the effectiveness would seem too high because of lack of frankness of those who "did not get caught." Large abdomens help greatly to bring out contraceptive truths.

Comparisons of various contraceptive series are much more satisfactory when the author clearly defines the population included in his calculated birthrate and the method of his selection.

As shown in FIGURE 1, any total population will be reduced by a number of restrictions related to contraception. Pregnancy rates may be calculated for any of the following groups:

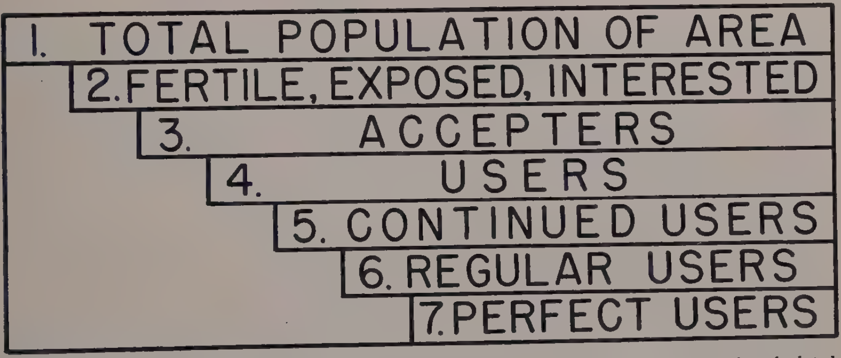

FIGURE 1. Portions of population for which pregnancy rates affected by contraception may be calculated.

1. The total population of an area. Results of any survey will be more applicable to other areas if the contraceptive to be tested is offered to every family in the area studied and the proportion accepting it for trial is recorded.

2. Those interested in contraception. This group includes only those who are exposed to pregnancy who consider themselves fertile and who do not wish to become pregnant.

3. Those accepting contraceptive supplies. The proportion of these will vary with the intensity with which contraception is made accessible, offered, or urged. The proportion of subsequent users will probably vary inversely with this intensity.

4. Those who, having accepted contraceptive supplies, use them at least once.

5. Those who continue to use them (with varying degrees of regularity) until the final interview or until a time when they decide not to use them again. It is probable that this group can be identified with greater certainty than the more restricted groups yet to be mentioned.

6. Those who use the method on every occasion of need.

7. Those who use the method according to instructions, that is, with perfect technique, and on every occasion.

Each of these groups will contain a certain proportion who are not accessible for a final interview. If this is because of death or moving to another area, it will probably not distort comparisons between different series.

If, however, exclusion from a group can be related to becoming pregnant, serious errors may creep in. If only those returning to a clinic are considered, for example, those becoming pregnant will not be brought back by the need for supplies and may stay away because of the dissatisfaction with the method which has failed.

It cannot be too strongly emphasized that accurate estimates of the results require direct contact with every accessible patient with follow-up home visits made to all those who have not otherwise recently reported or been interviewed.

For reasons previously given, the exclusion of patients from the "regular" or "perfect" class is peculiarly fraught with danger, however careful and unprejudiced the investigator may be. The terms "patient failure," "method failure," or "real failure," should be looked on with caution or suspicion.

While pregnancy rates for each of the groups named may be useful if a clear definition of the group is given the reader and that definition rigidly used in classification, the one most free of error appears to be that of the continued users, even though their regularity may vary. In publishing the results of a condom series, Tietze and Gamble[1] chose this group, including all pregnancies occurring prior to the final interview or the time when the couple decided never to use the method again. The findings showed the marked effect which interest in contraception can have on pregnancy rates. For those having made previous spontaneous efforts at contraception, the post-instruction rate was 6 per 100 years exposure. For those with no previous contraceptive efforts it was 16, and 11 for the entire group.

The rates for each group will be lowered somewhat by couples who are sterile, but who have not recognized the fact. Presumably, this small difference will be the same in most series, resulting in no great error in comparisons.

Of great importance in establishing the proportionate size of each of the given groups is the acceptability of the method in question. The less satisfactory the method, the fewer will be those who accept, use, continue to use, or use it perfectly. Since the overall affect on the total population is the more important in evaluating a method, comparisons of pregnancy rates on the groups named earlier, the total population, the acceptors, and users are preferable to those on the restricted group of regular or perfect users. Abstinence, for example, is completely effective for the "perfect" users, but is far from being so among the total population or the users.

It is not clear to which of the named groups the results of the series reported should be ascribed. They approximate those of Dewees and Beebe,[2] secured with diaphragms in an intelligent and spontaneously interested private practice. They found a rate of 6 per 100 years of exposure, with about half of the pregnant couples believing the conception was probably their fault. They resisted the impulse to call this a method failure rate of 3 since they did not know how many similar errors had been commited by the non-conceivers. Their article contains a valuable discussion of methods of evaluating contraceptive effectiveness.

Other investigators have found higher pregnancy rates for diaphragm users, the magnitude apparently affected greatly by the interest of the users in contraception and their reliability, and the number of pregnancies excluded because of irregular use. Low values reported are 7, 9, 9, 9, and 13 per 100 years exposure (3, 4, 4, 5, 4).

The results of a contraceptive study are more accurate if each patient can be studied for more than a brief period. Even without contraceptive protection, conception may not occur immediately and in some cases two months or more may be required before a pregnancy is certain. To attain desirable accuracy, the Council on Pharmacy and Chemistry asks that each case submitted in support of the effectiveness of a contraceptive material be followed twelve months or more.[6]

The investigation will have greater value if the ingredients and concentrations of the jelly-forming materials are given, as well as of those considered to be spermicidal. Future investigators can benefit little by the authors' careful and extensive study if it is not possible to reproduce the physical, as well as the chemical characteristics of the jelly which was used in the series of cases reported. The jelly-forming ingredients may also affect the contraceptive activity of the compounds which the authors have named.

In comparison with the diaphragm and jelly method, that of cream or jelly and syringe is thought by many to have greater acceptability. Insertion is easier and no postcoital extraction is required. For this reason it may prevent a greater proportion of pregnancies than would the diaphragm technique in certain populations, especially those without an intense desire for contraception.

The findings of the authors indicate that the effectiveness of jelly-alone, as they have measured it, is high. Whether it is higher than other series with the diaphragm method, when the same exclusions are made, is not clear. When one considers that with jelly-alone the spermatozoa may be deposited within a millimeter or two of the cervical mucus one can readily believe that occasional unintended invasions of the cervix may be possible, even though the environment produced by the jelly is unfavorable. With a diaphragm correctly placed the sperm must swim approximately 75 mm. or 15,000 times their body-length, through a medium containing varying concentrations of spermicidal substances. Consideration of this difference in length of route makes it seem inconceivable that the protection of a contraceptive jelly or cream alone can equal that of the same material used with a diaphragm.

Where avoidance of pregnancy is important, therefore, the added protection of a diaphragm should be prescribed.

Doctors Hunter, Darner, and Gillam and Dr. Stromme are to be commended for their study in this difficult and all-too-little ploughed field of preventive medicine.

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RECENT TRENDS IN THE STUDY OF INFERTILITY

By M. Edward Davis

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It is fitting that the problem of infertility be considered in a conference on world population problems. As scientific workers, our interest in the peoples of the world who cannot have children should be as great as in those individuals who are endowed with unusual fertility. The stability, the happiness, the social adjustment and even the economic productivity of the family unit depend in a large measure on children. The sterile couple is an important medical and sociological challenge to all of us who are interested in improving the lot of the world's population.

The study of human infertility has made great strides in recent years. It is only a short time since the story of human reproduction has been removed from the shrouds of mystery, legend, and folklore, and put on a scientific basis. Although there are large gaps in our knowledge, we have acquired a fair understanding of the physiology, we recognize some of the failures of this important function, and we can even remedy some of these failures.

In order that we may present an interesting and lucid account of some of the problems of human infertility, it will be necessary to describe the organs of reproduction and their function. Human reproduction, as well as that in most other species, high and low, requires the production and union of eggs and sperm cells. In order to make this possible, an elaborate set of organs and an intricate regulatory mechanism are necessary. The demonstration of their adequacy, anatomically and functionally, constitutes the study of sterility.

The female gonads have a threefold function: (a) they provide the ova or eggs for reproduction; (b) follicle growth and maturation produce the hormones necessary for adolescence and maturity of the individual, as well as the development and maintenance of the reproductive organs; and (c), the corpus luteum provides the special pregnancy hormone necessary in the preparation for, and the early development of, the fertilized egg. These several functions are closely integrated and the failure of one may lead to other failures.

Most anatomists have assumed that the primary follicles present in the ovary at birth provide the complete storehouse of ova for the entire reproductive lifetime of the individual. Evans and Swezy[15] have challenged this view and have demonstrated that in the rat, the dog, the monkey, and possibly in the human, new follicles are formed from the germinal epithelium as part of the reproductive process. They believe that ova in adult life are new formations which are created constantly by the germinal epithelium.

When the author was working with Hartman at the Carnegie Laboratory of Embryology in Baltimore, an unsuccessful attempt was made to answer this question. The germinal epithelium was removed mechanically from the ovaries in one breed of rabbits and buttered on the ovaries of another breed. Ovogenesis was studied for a clue as to the role of the germinal epithelium. More recently, we have devised a technique for destroying all the germinal epithelium by covering the ovary with a cellophane hood or by spraying it with a liquid plastic which will induce a fibrous capsule. This leads to the destruction of the surface epithelium. These experiments are still in progress, but thus far they have not proved conclusively that ova are not formed from germinal epithelium.

Potter and Davis[25] have examined many ovaries from women of all ages and have not been able to find support for the idea that, in the adult, new ova are being formed from the layer of cells covering the surface of the ovary. New formation of ova can be found occasionally in the ovaries of the infant up to one year of age, but after this time no new ova are apparent. We must conclude that the ova present at birth probably represent the total supply for the entire reproductive period of the individual.

Follicle activity continues in a desultory manner during the years prior to puberty when active follicular development is initiated. The stimulus for the onset of ovarian function is provided by the anterior lobe of the pituitary gland. It is not known definitely whether the ovarian follicles are not susceptible to gonadotropic stimulation prior to puberty or whether the pituitary is incapable of producing an adequate amount of gonadotropic hormone. This question should be answered by the study of a group of prepubertal and adolescent girls.

Several years may elapse before the mature pattern of ovarian activity develops. This adolescent phase is characterized by irregular menstrual periods, anovulatory in character, and by an absence of fertility. It provides for a period of somatic growth so that the reproductive organs may reach a mature state. As a result of more extensive follicular activity, increasing amounts of estrogenic hormone are made available. This growth-promoting hormone leads to the development of the normal skeletal pattern and stimulates the growth of the secondary sex-characters as well as the reproductive organs.

Maturity is heralded by the appearance of ovulatory cycles. Normal ovarian activity should continue during the active reproductive years to be interrupted by pregnancy, some local or systemic disease, or some endocrinal dysfunction of the regulatory mechanism.

The menstrual pattern is an excellent index of ovarian activity. The woman whose menses recur at fairly regular intervals is likely to have few anovulatory periods. It has been estimated that no more than two per cent of the periods of a normal fertile individual are anovulatory in character. The individual who has irregular menstrual periods, however, with long intervals of amenorrhea, usually has a high incidence of anovulatory cycles. In a group of 425 infertile women, Halbrecht[19] found 18 per cent of 1184 cycles were not associated with ovulation.

The length of the reproductive lifetime varies considerably in different women. Race, environment, nutrition, and general health are important factors. The usual length is somewhere between 30 and 40 years, averaging about 33 years.

Fertility, likewise, varies tremendously both in different individuals and in the same individual. There is good evidence that the peak of fertility is reached in the late 'teens and the early twenties. There is a decline in the thirties and a rapid dip as the menopausal period is approached. At the end of the reproductive period anovulatory cycles increase in frequency and soon ovulation ceases entirely.

There may be an interval of several years or longer during which ovulatory cycles are present and menses are fairly regular but fertility has disappeared. Many women have regular menstrual periods until 50 or 55 but they do not conceive. It is rare for a woman over 45 years old to become pregnant. There were only two women of 47 and 48 years who delivered babies in 100,000 deliveries at the Chicago Lying-in Hospital. We have studied many of these cycles in the twilight of the reproductive lifetime and a good number are ovulatory. Ova produced at this period in life must lose their ability to be fertilized. Obviously, it does not suffice to demonstrate that ovulation does occur, for there are other less tangible factors which are important in normal fertility.

The Study of Ovarian Function

The story of ovarian function must be accomplished to a large extent in an indirect way. It would be helpful if, in routine fashion, we could visualize the rupture of the ripe follicle and its safe transport into the fallopian tube. This has been witnessed in a few instances but in the human we must satisfy ourselves with the study of the cyclical changes induced by ovarian activity.

The exact mechanism of ovulation in the human is not known; and it is not the cataclysmic event that has been described in some of the laboratory animals. Burr[3] and his colleagues described electric potential changes which occurred simultaneously with ovulation in several women. This physical means of detecting the climax in follicular activity would be an important aid in studies in infertility, but there has been no confirmation concerning its usefulness. Electric potential changes induced by this physiologic event must be so insignificant that they are overshadowed by other environmental activities.

Direct inspection of ovaries has been possible on rare occasions at the time of laparotomy. Much valuable data has been accumulated by the study of ovaries *in situ* and their histological examination following their removal. Brewer and Jones[2] correlated ovarian changes and other data concerning cyclical activity. The author has collected a large series of human ovaries or liberal biopsies removed during the cycle; pregnancy and the puerperium and their histological study by Witschi is under way at the present time. All this information adds to our store of knowledge but it has no immediate clinical application.

Decker[14] has developed an instrument, the culdoscope, which makes possible the observation of the ovaries *in situ* without much hazard or inconvenience. This instrument, which comprises an optical system and a source of light, is passed through a puncture hole in the vaginal vault and by use of the proper technique the ovaries can be visualized. This approach will provide much information concerning the process of ovulation and ovarian activity.

Endocrine Assays. Endocrine assays as a means of studying ovarian function have only limited usefulness clinically, although they provide important data. The chemical methods for estrogens are still in the experimental stage; and several new approaches such as the fluorometric method (Jailer)[20] and chromatography are promising.

The production of progesterone by the corpus luteum can be followed indirectly by the pregnanediol excretion in the urine for this metabolite is an index of progesterone production. There is some question as to when luteinization of the follicle wall begins but little progesterone is demonstrable prior to ovulation. The daily output increases until about day 22 or 23 of the usual 28-day cycle, when it begins to decrease in amount, disappearing about the time menstruation begins. The daily output is usually less than 10 milligrams and the total output, during the progestational period, averages about 50 milligrams. The appearance of urinary pregnanediol in appreciable amounts at about the time of ovulation is good evidence of follicle rupture and corpus luteum formation. Small amounts of pregnanediol may be present in the urine in the absence of ovulation. Davis, Test[13] and their collaborators have just completed a metabolic study of a group of young women with ovarian failure. The administration of adrenocorticotrophic hormone to these women resulted in the elimination of pregnanediol in the urine. As much as 13 milligrams was put out by one woman in 24 hours. Although this material appears to be pregnanediol we will have to wait for verification until it is purified and chemically characterized.

Gonadotropin assays are valuable in the study of patients with ovarian failure. They help to determine the source of the failure. If the ovary is primarily at fault, increased amounts of FSH are present in the urine. This is the typical finding in the patient who has had her ovaries removed and is in the postmenopausal period. Normal gonadotropin assays characterize ovarian failure secondary to malfunction of the anterior lobe of the pituitary gland.

Farris[16], in 1946, described a method of detecting ovulation by injecting two millilitres of morning urine subcutaneously in Wistar rats 22 to 25 days old. After two hours, the rats are killed and the hyperemia of the ovary is compared with a color chart. Normally, positive reactions are obtained for three or four days successively during the period of ovulation.

Endometrial Biopsy. The endometrium mirrors the cyclical changes in the ovary. During the proliferative phase, the estrogenic hormone provided by the growing follicles stimulates vascular growth. The increased blood supply plays an important role in the growth of the glands and stroma. The endometrium increases in thickness as the glands increase in length and the stroma cells increase in number.

No appreciable change occurs in the endometrium for 24 to 36 hours following ovulation. The follicle metamorphosing into the corpus luteum now provides increasing amounts of estrogenic hormone and for the first time progesterone, the pregnancy hormone. Under the impact of these steroids, there is increased growth of glands and stroma. The glands take on a tortuous appearance for the stromal proliferation does not keep pace with the growth of the glands. Secretory activity in the cells of the glands is evident in the basal nuclei and the vacuolization, which gives to the epithelium a moth-eaten appearance. The stroma cells increase in size and much edema is apparent (FIGURE 1A, 1B).

The last four days of the cycle are characterized by a decrease in the edema but continued predicidual changes in the stroma and glands. The onset of menstruation is heralded by the appearance of leucocytes in the stroma. The spiral arteries become dilated and small interstitial hemorrhages appear. Soon after the blood breaks through the epithelial surface and free vaginal bleeding ensues.

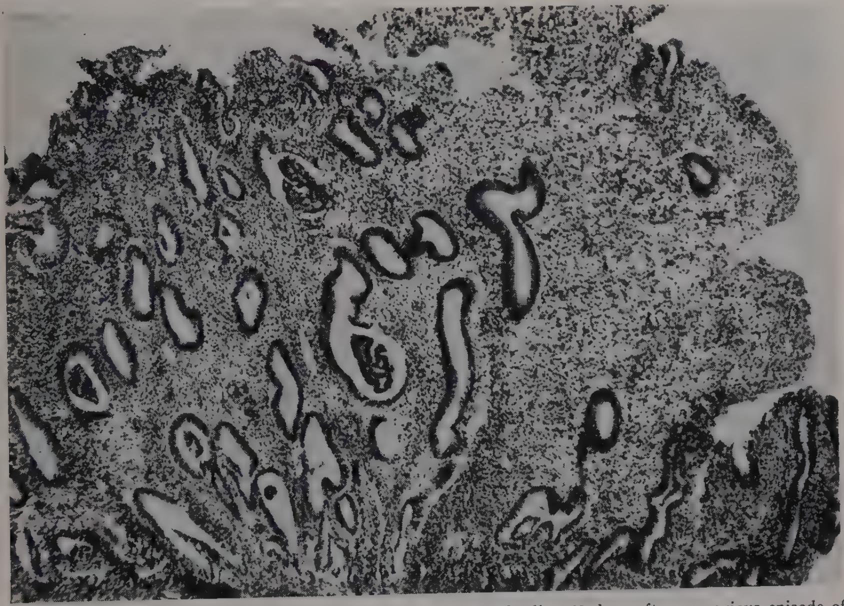

FIGURE 1A. Biopsy of the endometrium at the onset of bleeding 39 days after a previous episode of bleeding. The mucosa is in the proliferative phase and is indicative of an anovulatory cycle.

Endometrial biopsy is best obtained at the onset of bleeding even though the endometrium may show some necrobiotic changes and not be ideal from the histologist's viewpoint. One is certain that an existing pregnancy will not be disturbed once menstruation begins. Furthermore, the secretory changes in the endometrium are fully apparent and the diagnosis of an ovulatory cycle is certain. Unfortunately, endometrial biopsies reflect previous ovarian activity and provide little information about a current cycle. Nevertheless, serial biopsies will reveal an authentic story of ovarian function and endometrial response.

Does the endometrial picture provide information concerning corpus luteum function? It is possible for ovulation to occur, but corpus luteum development may be faulty and the production of steroids inadequate. This may result in disturbed motility of the fallopian tubes, inadequate preparation of the endometrium, and even unfavorable cervical mucus. Any one, or all, of these altered physiologic functions may decrease normal fertility. A careful study of the endometrium, including histochemical methods has provided new information which may help in our studies of infertility.

Cervical Mucus Changes. Another cyclical phenomenon which can be used to study ovarian function is the alteration in the quality and quantity of the cervical mucus which coincides with the time of ovulation. During the premenstrual phase the mucus is opalescent, contains polymorphonuclear leucocytes, and is of gelatinous consistency. At about the time of ovulation, the quantity may be increased ten-fold. There is a decrease in viscosity, probably as a result of an increase in water content, and leucocytes disappear. Originally described by Seguy and Vimeux[28] in 1933, these rhythmic changes in the character and the quantity of the mucus have been studied extensively by Pommerenke[24] and his associates, and correlated with the ovulatory temperature shift. Their endocrinal origin has been further confirmed by Abarbanel[1] in 1948.

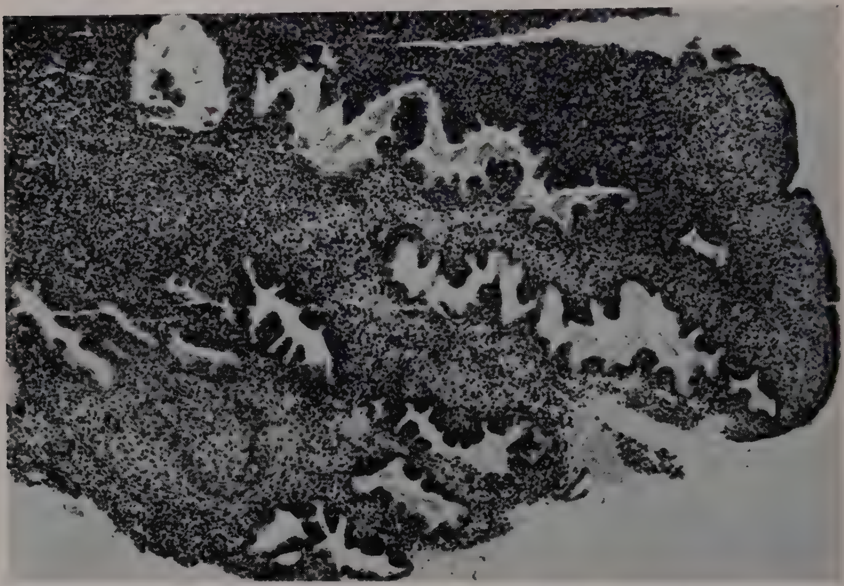

FIGURE 1B. Biopsy of the endometrium at the onset of bleeding in a woman with a normal menstrual pattern. The predecidual changes are evident in the secretory glands and stromal edema, characteristic of the ovulatory cycle.

Vaginal Smears. Cyclical changes in the squamous epithelial covering of the vaginal lumen have been demonstrated by various investigators. The mucosa is an extremely sensitive indicator of estrogenic hormone. Even local application of small amounts of estrogens provoke an immediate cell proliferation. Shorr[29] and his collaborators have demonstrated a sharp peak in the extent of vaginal cornification at the time of ovulation. This peak, however, represents estrogenic stimulation rather than a progesterone effect. Although a progesterone effect has been described, its appearance is not easy to recognize even by trained cytologists (Davis and Pearl).[9]

The vaginal smear is an excellent index of estrogenic activity but it is a poor criterion of ovulation. Serial smears should be studied in order to follow ovarian activity. The changing cytological picture may provide additional evidence of ovulation, but it alone is not diagnostic.

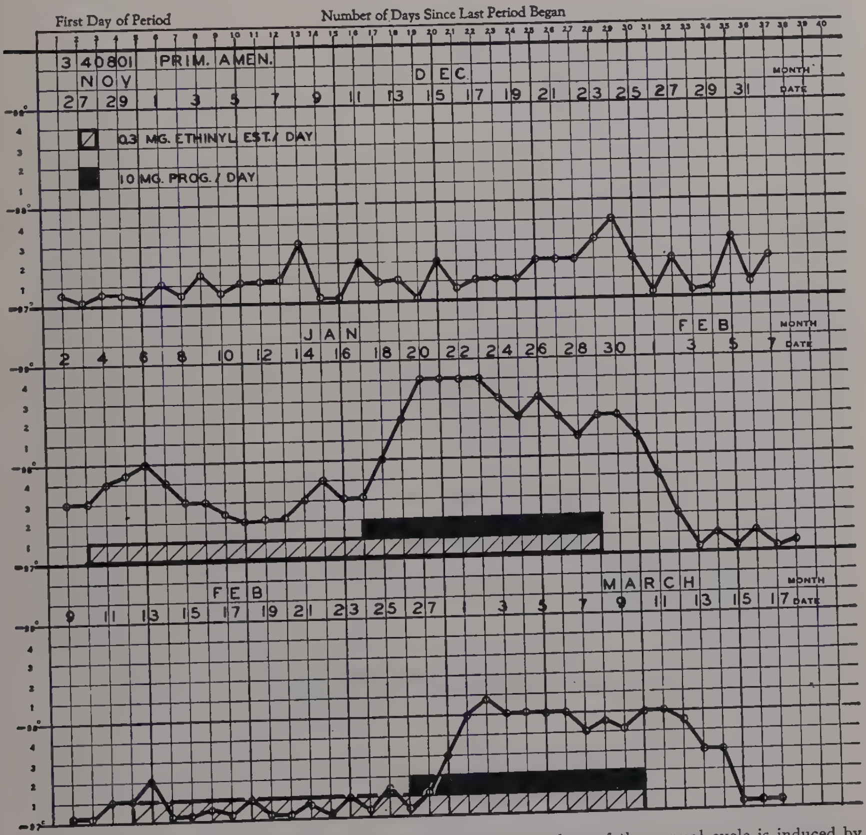

FIGURE 2A. The rise in body temperature during the last 14 days of the normal cycle is induced by progesterone from corpus luteum activity. In a young woman with primary ovarian failure the administration of estrogenic hormone did not alter the temperature curve but the administration of progesterone was followed by a prompt rise. The elevated temperature was maintained during the administration of the hormone.

Basal Body Temperature. Basal body temperature graphs provide the most simple and informative clinical record of ovarian activity and ovulation. Although temperature fluctuations during the menstrual cycle have been observed as early as 1904 by Van der Velde,[33] it is only recently that Tompkins[32] and others have popularized the application of this physiological observation in clinical use (Palmer)[23] (FIGURES 2A, 2B).

The cause of the temperature shift during the ovulatory period has been shown to be due to progesterone by Davis and Fugo.[8] These authors reproduced typical thermal changes in anovulatory and ovariectomized women by the administration of progesterone by several routes. The pattern of the thermal shift varies considerably in different individuals, rising abruptly in some and more slowly or in a step-ladder-like manner in others. The significance of these variations has been the subject of much study but, as yet, there are no good explanations.

The method of obtaining the temperature reading is not an important factor in an informative graph. Oral temperatures taken once a day, immediately on awakening, will reflect accurately the thermal changes induced in the normal woman by ovarian activity (FIGURE 3). Many extraneous stimuli induced by irregular living habits, undue mental or emotional upheavals, or other factors, may disturb the normal basal temperature pattern. A carefully prepared graph will provide much additional information for the physician such as the length of the cycles, the duration of the menstrual bleeding, and the sex practices of the family (Davis).[6]

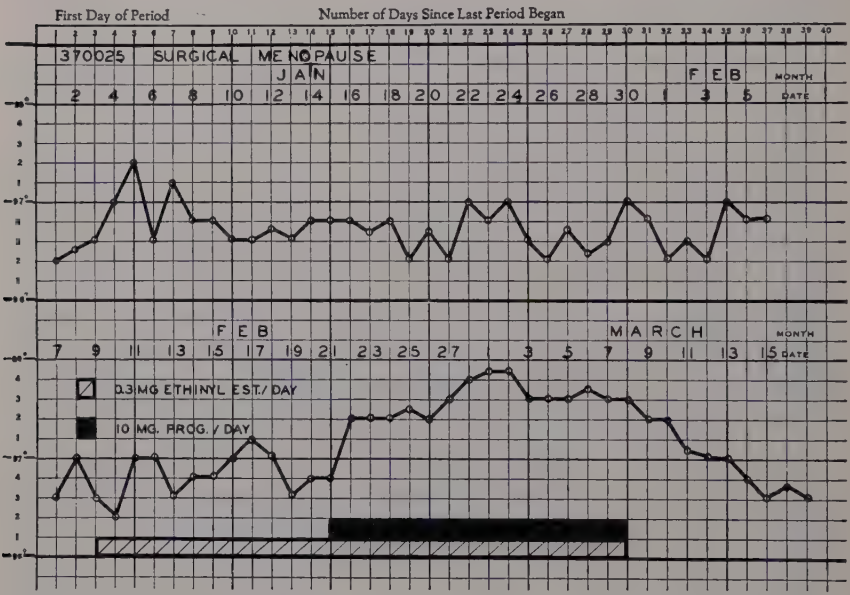

FIGURE 2B. A rise in body basal temperature was induced in a young woman who had her ovaries and uterus removed providing additional proof that progesterone is responsible for the rise in temperature.

The frequency and timing of coitus has an important bearing on fertility. In reviewing temperature records of many hundreds of families a pattern of sex life that favors infertility is found in at least a third of the records. Coitus at infertile intervals of the cycles, at too frequent intervals, or indiscriminately timed, may well decrease fertility. This is of particular importance in couples where the husband is of low fertility because of a diminished sex drive or his semen has a low sperm population and an increased incidence of abnormal forms. Proper medical guidance may increase fertility sufficiently to result in pregnancy.

The exact time of ovulation is not reflected in the basal body temperature graph. The early work in this field tended to implicate the lowest point in the temperature record prior to the ovulatory rise. Considerable data have accumulated to show that pregnancy can occur when intercourse has taken place during the entire period of transition from the low pre-ovulatory level to the elevated post-ovulatory phase. Although this clinical method of following ovarian activity may not reveal the exact time of ovulation, the period of the thermal shift nevertheless coincides with this important physiologic phenomenon.

Normally, the temperature begins to fall 24 to 36 hours before the onset of menstrual bleeding, reaching its lowest level during the menstrual phase (FIGURE 4). The maintenance of the temperature level beyond the date when the period is expected is a very significant sign of pregnancy. The continued survival and activity of the corpus luteum is now assured by the appearance of chorionic gonadotropin produced by the young chorion. Although the corpus luteum is not essential to the survival of gestation beyond its first four weeks of life, it will continue to provide hormonal support to the pregnancy until the placenta can take over the important function of steroid production. The post-ovulatory temperature level will be maintained during this entire period.

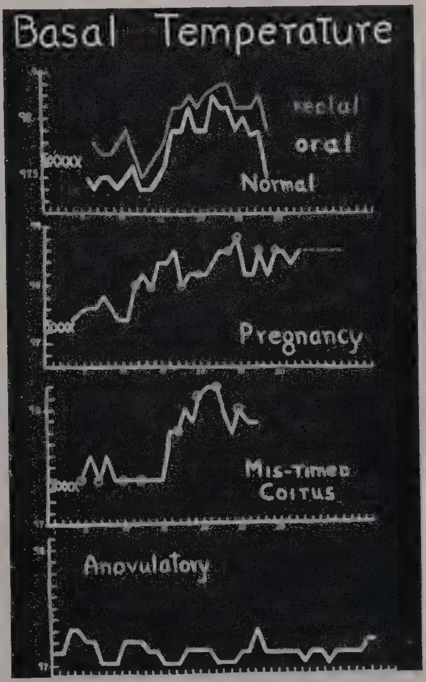

FIGURE 3. The body basal temperature record is a useful tool in the study and management of infertility. Oral temperatures taken on awakening each morning provide an accurate graph. The intelligent use of this physiologic phenomenon can be adapted to child spacing as well as to the study of ovarian function.

Ovarian Failure

Ovarian failure varies in degree. It may be mild and transitory and the patient may recover without therapy. A good many women have an irregular menstrual pattern and there may be long periods during which ovulation fails to occur. Such desultory ovarian function may be the result of local circulatory disturbances, hypothyroidism, constitutional disease, or other factors. It may become progressively more severe as a result of local ovarian dysfunctional changes which tend to produce many large and small atretic follicles, so-called cystic changes in the ovaries. It is frequently associated with functional bleeding and hyperplasia of the endometrium.

Ovarian failure may be primary as a result of abnormal gonads which cannot be stimulated by the hypophysis. Physiologically, in the postmenopausal period, the aging ovaries are refractory to all gonadotropic influences. Congenital abnormalities of the ovaries resulting in an absence of primary follicles are extremely rare, but more than 100 patients with congenital aplastic ovaries, associated with abnormal growth development, have been described. Most often, primary ovarian failure is the result of disease of the gonads produced by inflammation, dysfunction of the anterior lobe of the pituitary, or rarely, neoplastic changes. In these women, normal gonadal function may be difficult or impossible to restore.

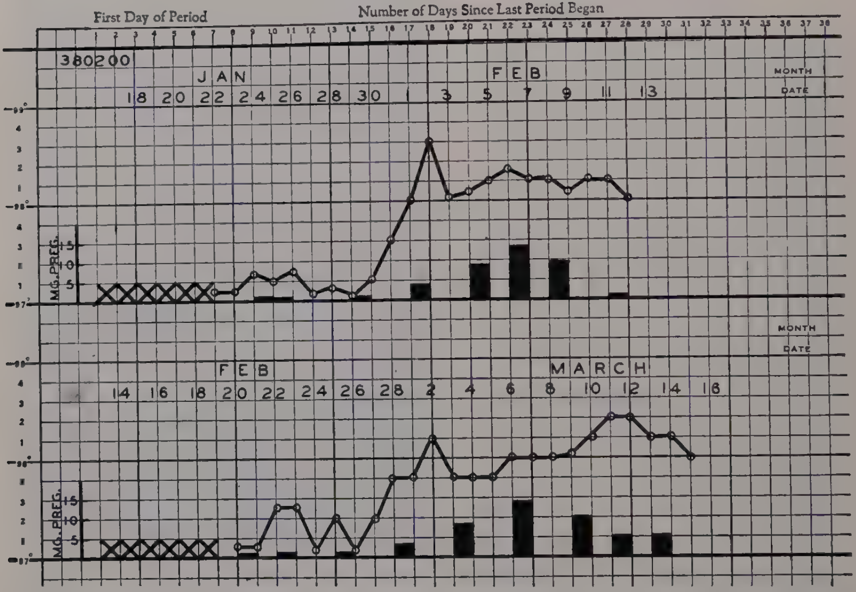

Figure 4. Two normal ovulatory cycles showing typical basal body temperature curves. Very little pregnanediol was present in the urine prior to the temperature rise following which the output ranged from 5 to 10 milligrams daily.

In most women, ovarian failure is secondary to abnormal hypophyseal function. The gonads are normal but there is an abnormal or deficient gonadotropic stimulation by the pituitary gland. This may be transient and brought about by failures in the supporting glands of internal secretion such as the thyroid or the adrenal. It may be the result of constitutional disease or serious malnutrition. It may be induced by the serious hemorrhage and shock which may occur following childbirth. Periods of ovarian failure, with its resultant disturbed menstrual function, may be short or long in duration depending on the underlying cause of pituitary failure.

More rarely, ovarian failure may be due to some inherent defect in the gonadotropic function of the anterior lobe of the hypophysis which results in permanent ovarian failure. These young women fail to undergo normal physical and sexual development; their reproductive organs remain infantile; they do not menstruate; they do not develop beyond the prepubertal stage; they cannot conceive. Thus far, it has not been possible to initiate ovarian function in these patients and our therapy has been substitutional. It has been possible, however, by means of estrogens to induce and to maintain complete physical and sexual maturity. Rarely, neoplastic disease of the pituitary gland results in failing ovarian function which may be extinguished completely as the condition progresses.

Endocrine Therapy

Ideal endocrine therapy, in ovarian failure and its resultant sterility, should consist largely of gonadotropins capable of stimulating cyclical changes in the ovary, resulting in maturation of the follicle and the discharge of the ripe ovum. Unfortunately, potent preparations that will accomplish these physiologic changes in the human are not available. Gonadotropic therapy in infertility due to ovarian failure has been disappointing. Three gonadotropic substances have been used experimentally and clinically (Davis).[7]

Chorionic Gonadotropin. Human chorionic gonadotropin is the oldest available gonadotropic substance but until recently, when very pure preparations became available, little was known about its physiologic function. It is fetal in origin, undoubtedly elaborated by the chorionic cells very early in pregnancy. It is present in the blood, placenta, and other body fluids and the urinary concentration in early pregnancy is extremely high. Although the average daily urinary excretion may vary from 10,000 to 20,000 units, in some women the daily output may be five or ten times as much. Potent commercial preparations are available and when they are administered to women they are non-antigenic.

Recent experiments have confirmed the fact that chorionic gonadotropin is entirely luteotropic. Its primary function is the maintenance of the corpus luteum if pregnancy occurs. If 10,000 to 20,000 units are injected daily in the woman who has an actively functioning corpus luteum, the menstrual cycle can be postponed 10 to 14 days. The corpus luteum fails to undergo regression and continues to flourish and produce progesterone which can be followed by urinary pregnanediol determinations. It can induce pseudopregnancy changes and a positive Aschheim-Zondek reaction. However, it does not affect the immature follicle in the ovary nor does it produce endometrial changes directly. Thus, the sole physiologic function of chorionic gonadotropin is to extend the life and function of the corpus luteum in the event of pregnancy; otherwise, it would undergo regression after its natural lifetime of 13 or 14 days and menstruation would ensue. The conceptus therefore assumes the responsibility of maintaining the corpus luteum and steroid production until the placenta develops sufficiently to take over this important function. In that it does not affect the human ovary, it has no clinical use in infertility due to ovarian failure. It may be useful in the treatment of early pregnancy failures that are the result of inadequate corpus luteum function. More work is needed to establish its value in these patients.

Equine Gonadotropin. In the mare, during pregnancy, a gonadotropic material appears in the blood, increasing in quantity as mid-gestation is approached. This serum gonadotropin may well be chorionic in character but unlike human chorionic gonadotropin, it does not appear in the urine. Equine gonadotropin will induce follicle growth, ovulation and corpus luteum formation in many of the laboratory animals as well as in some of the farm animals such as the sheep and the cow. In the monkey, it is predominantly a follicle stimulating factor. Its clinical use has been disappointing; although potent preparations which can be administered parenterally are available, there is little evidence that cyclical changes can be stimulated in women who do not ovulate. In normal women as in monkeys it is predominantly follicle-stimulating in character. The failure to affect the human ovary may be due to its animal origin and there is the possibility of antihormone formation.

Pituitary Gonadotropins. Crude extracts from the anterior lobe of the pituitary have been used in the laboratory for many years. Implants and extracts have completely replaced the action of the anterior lobe of the pituitary in hypophysectomized animals but these impure preparations cannot be used in the human. Commercial preparations of pituitary gonadotropins have been used extensively in ovarian failure of all degrees, but there is little evidence that they have stimulated gonadal activity.

Since 1934, Casida[5] and his co-workers have explored the action of unfractionated pituitary extracts on calves, cows, sheep and other animals. They have produced follicle growth, maturation of the ovum, ovulation, and corpus luteum formation. Super-ovulation occurred in many animals; and ova were fertilized and implanted in the uterus. In most instances, embryos beyond the average number of the species failed to develop to term, but it was felt that this was due to overcrowding and an abnormal environment rather than to hormonal factors.

Potent fractionated and unfractionated pituitary extracts developed by Meyer and McShan[22] have been used experimentally in our clinic with promising results. It has been possible to stimulate human ovaries in nonpregnant women during their active reproductive years, during pregnancy, and in the immediate postpartum period. These ovaries were removed for gross and histologic study. Follicles grew at an astonishing rate and rapidly passed from physiologic to pathologic proportions (FIGURE 5). Among the striking observations were the rapidity of gross ovarian enlargement and follicle growth. In several pregnant women who were to have therapeutic abortions there were follicles that appeared to have undergone recent ovulations. Unfractionated extracts were more potent than the fractionated material. The pituitary gonadotropin was administered subcutaneously as well as intravenously after the women were carefully tested for protein sensitization (Davis and Hellbaum).[10, 11]

Unfortunately, potent pituitary gonadotropins have not been available for clinical trial. Their complex protein character makes them difficult to isolate in pure form, nevertheless, some progress has been made. A pure follicle stimulating gonadotropin has been isolated from sheep pituitary by Li in 1940.[21] The luteinizing factor has been obtained in fairly pure form by Greep, Van Dyke and Chow in 1942,[18] and others. Perhaps the recent impetus provided by the isolation of ACTH may provide renewed efforts to develop a potent gonadotropic factor from the anterior lobe of the pituitary. Any real progress in the endocrine therapy of ovarian failure must await the isolation of potent pituitary gonadotropins.

Estrogens. The use of estrogens in ovarian failure has been largely substitutional. It has been repeatedly demonstrated that the ovary remains dormant under this form of therapy so that estrogens can achieve complete ovarian replacement with the exception of reproduction.

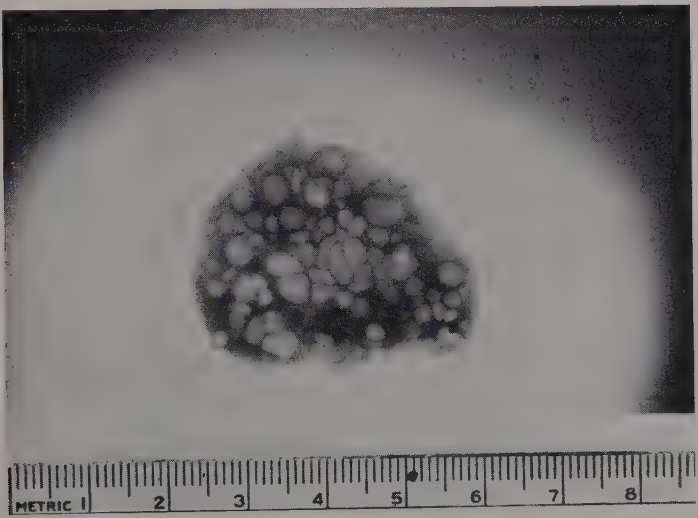

FIGURE 5. Translucent appearance of a cross section of an ovary removed from a young woman to whom an unfractionated gonadotropic pituitary extract was administered daily for six days. The ovary was increased greatly in size and weight and largely replaced by developing follicles, many of which showed a marked overgrowth of the granulosa.

There is evidence, however, that estrogens do influence pituitary function. Thus, the administration of a large dose of an estrogen early in the cycle will delay ovulation 10 days. Small daily doses (1 to 3 milligrams of diethylstilbestrol) throughout the cycle will inhibit ovulation. It has been suggested that small doses of estrogens be administered for long periods with the hope of stimulating the ovaries through their pituitary control. Although this therapy offers no promise in serious ovarian failure, it can be tried in mild ovarian failure.

Progesterone. Progesterone has likewise been suggested to enhance the gonadotropic function of the pituitary. The rationale in its administration is to supplement the endogenous secretion of progesterone so that the pituitary-ovarian interaction is more fully interrupted. The catabolism of the improved endometrium might exert a more effective toxic stimulation of the pituitary with a resurgence of FSH and renewed activity of the ovary. Six or eight injections of 25 milligrams of progesterone intramuscularly, beginning day 18 or 20, has been suggested.

It is possible that an inadequately prepared endometrium would make an unfavorable locale for implantation, thereby resulting in infertility in spite of fertilization. Although such a condition can theoretically occur, practically there are no good data to establish it. However, chorionic gonadotropin to stimulate corpus luteum function or additional progesterone should result in more favorable environmental conditions for implantation.

Thyroid Extract. The influence of the thyroid on gonadal function has been demonstrated by experimental and clinical data. The action of the thyroid on the ovary may be a direct one or through the pituitary, or it may be part of a general metabolic effect. Ovarian hormones likewise influence thyroid function.

Mild degrees of hypothyroidism which mildly alter the basal metabolic rate may result in transient ovarian failure. Gross hypothyroidism may be associated with severe degrees of ovarian failure; and thyroid medication should be tried in all women with ovarian failure for at the present time it is the most useful endocrine preparation we have clinically. Further studies of the thyroid-ovarian relationship in infertility should be made using serum iodine determinations, for the basal metabolic rate is a crude index of thyroid function.

The Fallopian Tubes

The fallopian tubes are integral parts of the reproductive passageway for they provide the avenue by which the spermatozoon can meet the ovum and the fertilized egg can be transported safely into the uterine cavity. Tubal failures are much more common than failures in ovarian function for they play a vital role in at least one-third of our sterile couples.

The mechanism by which the egg enters the ostium of the tube has been studied extensively. Although there is no direct connection between the rupturing follicle and the tube, its entrance into the ostium is facilitated by an ingenious mechanism recently observed in the human. Tubal peristalsis, which is accentuated at the time of ovulation, mobilizes the tubal ostium so that it almost engulfs the ovary at the site of rupture. Fluid currents established by tubal activity and the action of the cilia aid in directing the escaped ovum into the tube.

The ovum is fertilized in the tube and its transportation downwards into the uterine cavity is accomplished by the tubal contractions. The delay at the uterine end of the tube allows the blastocyst to enter the uterine cavity at a propitious time, but how this delay is accomplished is not known.

This normal physiology of the tube is important in fertility. Abnormalities of the tube resulting in interference with the patency or function decrease the likelihood or make it impossible for the sperm to meet the ovum and for normal transport of the fertilized egg into the uterine cavity. Most often, these abnormalities are the result of inflammatory disease to which the fallopian tubes are extremely vulnerable. Rarely, tubal anomalies interfere with normal function.

There are two standard procedures for determining tubal patency, uterotubal insufflation and uterosalpingography. The classic experiment in which Rubin in 1920 demonstrated the patency of the tubes by the passage of air through a cannula introduced into the cervix stands as a landmark in our modern sterility investigation. There have been many refinements added to this ingenious experiment but the basic principle remains unchanged.

Several years earlier, Cary[4] and Rubin[27] in this country carried out some independent studies on the use of radiopaque materials to visualize the uterine cavity as well as the tubes. It is now possible to demonstrate patency of the tubes and, at the same time, visualize abnormalities of the reproductive tract. In most clinics both of these methods are in use for they should not be looked upon as competitive procedures, as one supplements the other and both contribute to the comprehensive study of the sterile couple.

Uterotubal insufflation is best carried out during the several days following a normal menstrual period. There is little likelihood of interrupting an early gestation at this time. Furthermore, the endometrium is early in the proliferative phase and is less likely to be traumatized. The tubal activity is at a minimum and it is possible that the incidence of tubal spasm is reduced.

The only contraindication to this procedure is pelvic infection. Every attempt should be made to reduce this hazard to the minimum. An endocervicitis should be cleared up prior to the examination; and where there there is a history of a recent exacerbation of pelvic inflammatory disease the test should be delayed. It may even be desirable to use antibiotic therapy prophylactically for several days prior to the procedure in the individual with residues of pelvic disease.

Carbon dioxide gas under controlled pressure is allowed to pass through the uterus, tubes and into the peritoneal cavity. A kymographic tracing of gas pressures is an additional safeguard and it will show tubal peristalsis as well as abnormalities in tubal function. The escape of the gas from the tubes into the peritoneal cavity can be heard by the use of a stethescope on the lower abdomen. Shoulder pain coming on after the patient sits up is confirmatory evidence of the entrance of gas into the peritoneal cavity and its subdiaphragmatic accumulation. It can be repeated in the same patient at periodic intervals. It has therapeutic as well as diagnostic value. Almost 60 per cent of the women who conceive following an infertility study do so within four months following uterotubal insufflation with gas or uterosalpingography. By what mechanism uterotubal insufflation by gas or fluid medium improves fertility is not known. However, this procedure is undoubtedly the most important part of our infertility investigation.

It has been suggested that insufflation pressures could be increased safely to as much as 300 millimeters of mercury. Grant and Mackey[17] reported that in 41 per cent of 216 patients who had non-patent tubes patency was established using these increased pressures, and 18 per cent became pregnant after repeated insufflations. These results are better than those that have been reported following surgical salpinogostomy or lysis of tubal adhesions.

Uterosalpingography

The visualization of the reproductive tract is of value in most studies since it provides pertinent information concerning the uterus as well as the fallopian tubes. Malformations of the uterus of varying degrees are found in about eight per cent of patients in our clinic. In most women, they are of no clinical importance but in some cases complete duplication of the uterus is found. Small myomata and polyps of the endometrium are occasionally visualized.

The tubal lumens may show evidences of disease in local dilatation, partial blockade, or gross disease. The tubes may be elongated, closed, adherent, and their distal ends may be transformed into large sacculations as a result of previous inflammatory disease. The ends of the tubes may be open but their character may reveal tubal tuberculosis. Finally, neither tube may be visualized, the obstruction which occurs in the cornual portion prevents the radiopaque medium from escaping into the tube (FIGURES 6A, 6B).

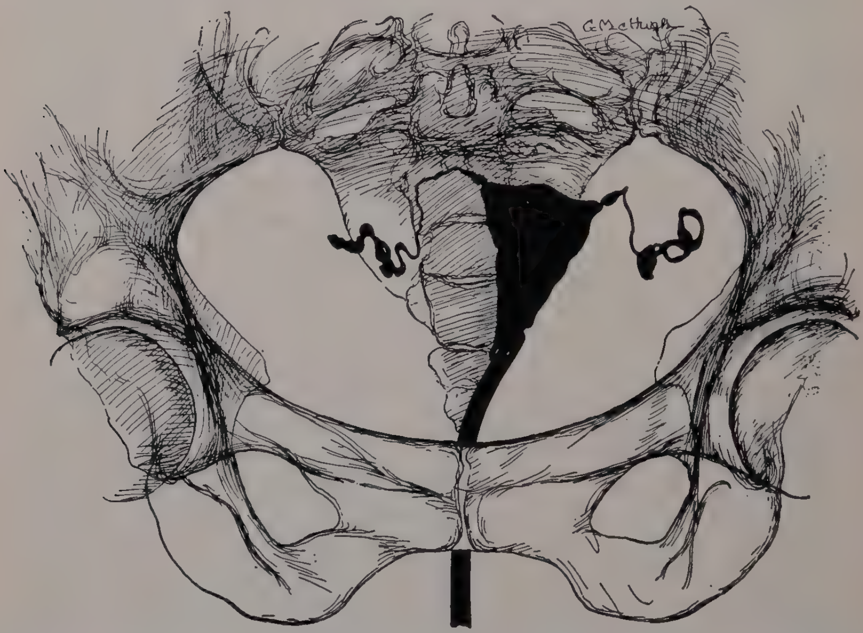

FIGURE 6A. Normal hysterosalpinograph. The uterine cavity and both fallopian tubes are completely filled and normal in appearance. Sphincter-like structures at cornual ends of tubes are visualized clearly.

All this additional information gleaned from the visualization of the reproductive organs compensates for the slightly increased hazard of introducing a liquid medium into the uterus and tubes. If the procedure is carefully carried out and the patients selected properly, the hazard of activating a slumbering infection is not great and use of careful technique will prevent the introduction of infection from without. It is possible to introduce oil into the circulation by trauma to the endometrium by the cannula tip, but if the procedure is carried out under fluoroscopic vision this complication can be recognized promptly and the injection discontinued before serious harm is done.

The use of a non-absorbable medium such as lipiodol has the disadvantage that it may be retained in tubes which are partially or completely obstructed. It may remain for long periods of time and occasionally its presence may provoke a foreign body reaction. Absorbable media have been suggested, and are in use, but these provide poor visualization. Their rapid disappearance often defeats the purpose of salpingography. If a non-absorbable medium is used, a single examination should suffice, and if additional uterotubal insufflations are necessary, only carbon dioxide should be used.

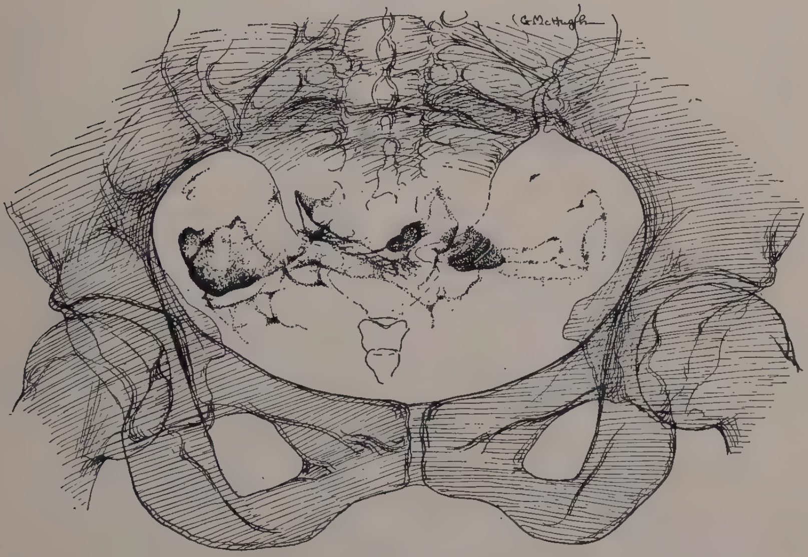

Figure 6B. Roentgenogram of the same patient 24 hours after the injection of opaque oil. Note the characteristic spread of the contrast medium among pelvic cavity viscera indicative of tubal patency.

The Speck Test

Speck in 1948[30] suggested an ingenious method for establishing the presence of tubal patency. Phenolsulphonphthalein is injected into the uterine cavity. If the fallopian tubes are patent, it escapes into the peritoneal cavity from which it is rapidly absorbed and appears in the urine within thirty minutes. It is easily recognized in alkaline urine. If the dye fails to be excreted within the time limit, the tubes are probably closed for the dye is absorbed very slowly from the tubal lumen. Speck in 1950,[31] reported an accuracy of 100 per cent in 210 tests carried out by him and other investigators.

Davis, Ward and King[12] recently investigated this test in a group of patients. They found that it provided accurate information concerning tubal patency in 85 per cent of cases studied. There were false positives as well as false negatives. The safety, simplicity and economy of this new procedure, however, recommend it for further study and investigation. Although it will not replace uterotubal insufflation and uterosalpingography, it may find a useful place in our procedures for the investigation of infertility.

The Treatment of Abnormalities of Tubal Patency

The prevention of tubal blockade has been a major goal since the advent of antibiotic therapy. Gonorrheal infections can be eradicated successfully when the disease is limited to the lower genital tract. The early therapy of gonorrheal and post-abortal salpingitis will decrease the residual tubal damage which is responsible for tubal closures.

Partial tubal blockade may be due to obstructions within the tubal lumen or adhesions of the tube to the environmental structures. Such constrictions and fixations interfere with the normal peristaltic action of the tubal musculature as well as with tubal patency. Although the lumen may be patent to a gas or fluid, the interference with tubal function may decrease fertility in the individual.

Partial tubal blockade may be treated by uterotubal insufflations of carbon dioxide, repeated every two or three months. The pressure under which the gas enters the uterus should be carefully controlled so that no serious damage will result. How often one is able to overcome partial obstructions is not known, but it is certain that some of these individuals become pregnant after repeated efforts.

Complete closure of the fallopian tubes provides a permanent barrier to conception. Rarely will patency be restored spontaneously. Surgical procedures to restore tubal patency have resulted in so few pregnancies that many physicians have been discouraged but new techniques in surgery and a marked decrease in the hazard of all surgical operations have rekindled interest in this problem.

Recent experiences in tubal plastic surgery have emphasized several important facts. Tubal patency should be restored by the simplest surgery possible, for the more extensive the procedure the poorer the results. The proximity of the tubal ostium and its adjacent ovary should be maintained. This is necessary to facilitate the normal transport of the ovum into the oviduct. The restoration of patency to the tube does not mean that the oviduct has been restored to normal. The lumen may be tortuous and lined by many pockets and crypts which interfere with the meeting of sperm and egg. Tubal epithelium may be largely destroyed and the peristaltic action of the musculature grossly altered. Thus, the restoration of patency does not assure normal fertility.

Tubal closures at the ostium offer the best prognosis. After the closed end has been opened, patency may be more easily maintained by the use of an absorbable cone-shaped tube inserted into the fallopian tube. These absorbable tubes disintegrate in about two weeks at which time healing should have taken place. Where the blockade is at the uterine end, the tube must be severed from the uterus, its patency checked, and then it must be reinserted into a new opening in the cornual portion of the uterus. It has been difficult to maintain tubal patency in these implantations. A plastic tube of very narrow diameter, however, can be threaded into the severed portion of the fallopian tube and the end fed into the uterine cavity. This plastic tube may be left *in situ* for two or three months, when it can be removed through the cervical os of the uterus without difficulty. This procedure assures tubal patency. Uterotubal gas insufflations following salpingostomy will aid in maintaining a patent lumen.

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Discussion of Paper by Doctor M. E. Davis

Doctor William B. Stromme, *Minneapolis, Minn.:* Dr. Davis mentioned the important work of Dr. I. C. Rubin. For purposes of the records and for proper credit, I would like to mention that the pioneer studies on tubal patency, that of salpingography using radio opaque material, were carried out by Dr. William Cary of New York and reported in 1914.

RECENT TRENDS IN THE STUDY OF INFERTILITY

By Charles M. McLane
Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital

The subject of female infertility has been divided into two parts by previous papers. Essentially, this paper will be concerned with emotional factors in infertility as well as with the part played by abnormalities of the cervix and uterus. Emphasis will be placed on changes in thought and therapy rather than on accepted knowledge and technique.

Estimates of the percentage of success in treating the infertile couple are varied, but 30 per cent is a good average. In 15 per cent of those cases in which our treatment fails, both husband and wife are adjudged to be normal by present diagnostic methods. Why does this high percentage exist of apparently normal couples who cannot have children? One obvious reason is that, in the case of many of these couples both partners are relatively infertile. Presently the only true test of fertility is the number of children produced by a given couple. Stock breeders, and others working in the field of animal husbandry, have clearly shown by cross-breeding that the fertility of individuals in a species varies considerably, but that it can be accurately determined. Our present laws rather frown on cross-breeding among humans, but if a test for relative fertility could be devised, perhaps prospective spouses would be so selected as to eliminate most of the 15 per cent of infertile but normal couples.

Only in the past five or six years has any serious thought been given to the fact that an emotional disturbance, a neurosis, or even a psychosis may prevent conception. Even today, many infertilitists refuse to recognize the fact that emotional and mental changes can operate against the possibility of conception. Ovulation, fertilization and implantation are very delicate processes which demand the co-ordination of many anatomical and physiological functions. What if the tube is in spasm or its cilia waving in the wrong direction at the crucial moment of migration of ovum and spermatozoa? What if the cervical mucous or endometrial secretion are antagonistic at just the time spermigration is taking place? These distortions of natural re-action may occur monthly in an emotionally disturbed woman.

Reports in recent medical literature show that consultation with a psychiatrist, and, if necessary, subsequent psychotherapy, is of marked benefit. One clinic has estimated that 20 per cent of its successes are the result of its routine employment of psychiatry. It is our feeling that some of our infertility patients try too hard to become pregnant and worry too much about their inability to do so; many women, who seem outwardly anxious to have children, are subconsciously rejecting the whole idea. Often, in talking to those patients, one finds that the expressed desire for children stems from the urging of relatives or from feeling of inadequacy forced on them by social pressures. Every good infertility clinic should have a psychiatrist as an integral part of it, one who gets to know the patients during the regular visits, and whose presence is taken for granted.

Authorities have agreed for some time that severe cervical infection or extreme stenosis may cause infertility. The thought is relatively new, however, that minor alterations in the physical characteristics and the chemical and bacteriological constituents of the cervical mucous can also act as preventives to conception. Tortuosities of the cervical canal and minor stenoses play their part as well.

Cervical mucus goes through a definite monthly cycle, as does the endometrium. About the time of ovulation it is more abundant, clear, and quite thin, containing very few cells and being free of pus. This mucus comes from several sources: first, the cervical glands; second, the endometrium; and third, probably from the peritoneal fluid that is drawn into the tube at ovulation and passed along through the uterus into the cervix. Therefore, the alteration in function of any part of the generative tract may change the amount and consistency of cervical mucus. This mucus is thought to be necessary for proper sperm migration, and possibly for the nourishment of the spermatozoa.

Abnormal chages in the cervical mucus are believed to be brought about in one of two principal ways: (a) by the presence of a low grade infection in the cervical glands, causing them to produce a thick, tenacious infected mucus; or (b) by changes in the hormone balance of the individual which result in a cellular, scant, and often thick mucus. Either of these abnormal types of secretion inhibits or prevents spermigration. Investigative work is aimed at determining the causes of infection or hormonal imbalance, and at suggesting subsequent treatment. W. T. Pommerenke and his co-workers have published several interesting papers on the chemical constituents and physical characteristics of the cervical mucus. E. Lee Buxton has shown that certain bacteria are spermicidal even in normal mucus. Edward Hughes has recently demonstrated that lack of sufficient amounts of estrogen and, in some cases, of progestin, may affect the glycogen metabolism of the endometrium as well as the amount and consistency of the cervical mucus. The Huhner or postcoital test, done several hours after intercourse at ovulation time, allows an examination of the mucus to determine whether it is normal and whether spermigration is taking place. The postcoital test is best performed four to six hours after intercourse rather than immediately after it. Our therapy has attempted principally to clear up the immediate infection, reserving endocrine treatment for those cases which fail to respond to antibacterials. It is first necessary to eliminate any stenosis and allow free drainage from the entire cervical canal. If erosions present on the vaginal portions of the cervix do not respond to antibacterial therapy, they are coagulated. We feel strongly that coagulation of the cervical canal should be restricted to extensive infection, and should not be employed in cases of low grade infection, where the only symptom is alteration in the cervical mucus. An older form of treatment consisted of the cervical canal and application of mild antiseptics such as 2 per cent mercurachrome or ½ per cent silver nitrate. As one after another of the "wonder drugs" came along, each was tried in turn. Sulfa helped either by mouth or by vaginal instillation, penicillin, either in suppository or injection form, proved more efficacious. Most recently, aureomycin powder with anti-monelia and anti-trichimonas powder added is applied locally by tampon or cervical cap, and has given the best result. Those cases which do not respond to this last therapy are treated with small doses of estrogens in the first half of the menstrual cycle. The improvement in the treatment of cervical factors in infertility has yielded the greatest increase in our percentage of successes in recent years.

A greater emphasis has been placed on the part played by mal-positions of the uterus as a cause of infertility. The routine suspension of every retroverted uterus (regardless of the cause of the back-ache), practiced up to about twenty years ago, caused this operation to fall into disrepute. Dilatation and curettage, cauterization of the cervix, suspension and appendectomy were done so often as one procedure, and for so little reason, that facetious members of house staffs used to refer to this operation as "The Blue Plate Special." Today's feeling is that when every other cause of infertility has been eliminated and the patient has a retroverted uterus, a pessary should be inserted. If pregnancy does not result, only then should a suspension be done. A suspension should always be performed if the uterus is adherent in retroposition. Many cases of unsuspected endometriosis are discovered at the time of operation. It is quite possible that, in a retroverted uterus, the endometrium is congested and not capable of receiving the fertilized ovum and allowing its implantation. The careful selection of cases for suspension will cure a certain number of infertile women.

Endometriosis as a cause of infertility has been receiving a little unnecessary publicity in the lay press. There seems no doubt that this condition is increasing and that, in some cases, it is cause of infertility. It is debatable whether we are justified in urging all married couples to have children when they are first married simply to prevent endometriosis from developing. In the already infertile female, endometriosis should always be ruled out, either by the use of the culdoscope or, if there are clinical evidences of the disease, by abdominal operation. Conservative surgery is indicated, usually consisting of the removal of any cysts without sacrificing the ovaries, cauterization of all implants and suspension of the uterus. Attempts to become pregnant should follow immediately after the operation. In known cases of endometriosis, diagnosed either by culdoscopy or at previous operation, the use of testosterone therapy has been recommended by some authors. Sufficient testosterone is given to make the patient miss two or three menstrual periods and she is advised to attempt pregnancy as soon as therapy is discontinued.

These abnormalities of the endometrium associated with abnormal ovarian function have been discussed previously. A few conditions, such as chronic endometritis, chronic passive congestion, and the already noted incomplete glycogen metabolism deserve some mention. All of these conditions may be diagnosed by endometrial biopsy. Chronic endometritis can be eliminated by dilatation and curettage, and by improving the patient's general health, with emphasis upon especially large doses of vitamins. Chronic passive congestion is usually associated with retroposition and responds to essentially the same treatment. According to Dr. Edward Hughes, incomplete glycogen metabolism occurs in cases of infertility and habitual abortion. A diagnosis is made by special staining of the endometrium removed at biopsy, and the results of treatment are evaluated by repeated biopsies. Treatment consists of small doses of stilbestrol (1/10 mgm. a day for 14 days); and for those cases which do not respond, estrogen in the first half of the menstrual cycle and progestin in the second. This therapy has also been used empirically without biopsies on those patients whose temperature charts showed a slow and unsatisfactory post-ovulatory rise or a poorly sustained rise.

Tumors of the uterus, principally myomata and polyps, may prevent conception mechanically by distorting the uterine cavity, disturbing the endometrium and keeping the cervix out of the seminal pool. These tumors can be diagnosed at the time of curettage, by hysterography or by pelvic examination, and their removal is indicated. It is now believed that the presence of a fibroid, even if it causes none of the above complications, yet may influence fertility. If all tests are normal and a fibroid is present, myomectomy is usually recommended and the patient urged to attempt pregnancy immediately after the operation.

The role of so-called hypoplasia of the uterus is a questionable one. The diagnosis is often made too glibly on the basis of a supposedly small uterus. Many patients are permanently emotionally disturbed by having been told that their female organs are under-developed. If a patient menstruates regularly, ovulates regularly and has normal secondary sexual characteristics, the size of her uterus is of little importance. Naturally, there are definite cases of hypoplasia, but these should be associated with scant irregular periods and lack of development of secondary sex characteristics before any diagnosis of hypoplasia is made. Treatment of this condition, when it does exist, is generally unsatisfactory, but some form of hormonal therapy should be tried.

Advances in the field of infertility are slow, and progress is often discouraging. Sometimes it seems as if pregnancy, when it does come about, occurs in spite of, rather than because of, professional skills; but, with growing appreciation of the need for consideration of the patient as a whole, the purely gynecological aspect of the problem is on the way to solution.

Summary

Doctor Carl G. Hartman, *Ortho Research Foundation, Raritan, N. J.*: Shall we, then, continue to give thought to the basic questions raised—problems that must be solved if world tensions are to subside and if the world is to become a home of peace, security and plenty? The time has arrived when the world must call a halt to overpopulated countries which try to solve their own problems by confiscating lands of weaker nations.

The Western world, while it has invented engines of destruction, has also advanced medicine, hygiene and sanitation. By advancing biological discovery, we have conquered pandemics, reduced infant death, prolonged life. Man, the rebel, has rebelled against the inevitability of dying. Now, to preserve the balance and insure the necessities as well as comforts of life for all peoples, he must rebel also against being born. This is the crux of the matter: being born is not nearly as inevitable as dying.

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